Molecular diversity of the base-promoted reaction of phenacylmalononitriles with dialkyl but-2-ynedioates

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Abstract

In the presence of tetrabutylammonium bromide (TBAB), the cycloaddition reaction of phenacylmalononitriles with dialkyl but-2-ynedioates in acetonitrile at room temperature resulted in 3,3-dicyano-5-hydroxy-5-arylcyclopent-1-ene-1,2-dicarboxylates in high yields. More importantly, the DABCO-promoted domino reaction of two molecules of each phenacylmalononitrile and dialkyl but-2-ynedioate in acetonitrile at room temperature afforded unique multifunctionalized carboxamide-bridged dicyclopentenes in moderate to good yields and with high diastereoselectivity.

Introduction

Phenacylmalononitrile is one of the privileged functionalized compounds [1-5], because it contains one carbonyl group, two cyano groups, and an activated methylene unit. Phenacylmalononitrile exhibits versatile reactivity, high synthetic efficiency and molecular diversity and has been widely employed in many synthetic reactions [6-10]. On the other hand, phenacylmalononitrile is also a readily available substrate, which can be easily prepared through a base-promoted substitution reaction of phenacyl bromide with malononitrile under mild conditions [11-16]. In many practical cases, phenacylmalononitriles could be conveniently generated in situ by directly using a mixture of phenacyl bromide and malononitrile in the reaction system [17-22]. As a consequence, the unique features of phenacylmalononitriles make them good candidates for the efficient construction of diverse carbocyclic and heterocyclic compounds [23-30]. For example, Han and co-workers successfully developed a tetrabutylammonium fluoride-catalyzed cycloaddition of phenacylmalononitriles and nitroolefins for the diastereoselective synthesis of multifunctionalized cyclopent-2-ene-1-carboxamides [31] (reaction 1 in Scheme 1). Liu and Ban furnished a chiral thiosquaramide-catalyzed tandem Michael–Henry reaction of phenacylmalononitriles and nitroolefins for the enantioselective synthesis of cyclopent-3-ene-1-carboxamides [32] (reaction 2 in Scheme 1). Mohanan
Scheme 1: Representative cycloaddition reactions of phenacylmalononitriles.

Results and Discussion

Initially, the reaction conditions were briefly optimized by using \( p \)-methylphenacylmalononitrile (1a) and diethyl but-2-yneedioate (2a) as standard according to the previous reported work [31]. In the presence of potassium carbonate and tetrabutylammonium chloride (TBAC), the reaction in acetonitrile at room temperature gave diethyl 3,3-dicyano-5-hydroxy-5-(\( p \)-methylphenyl)cyclopent-1-ene-1,2-dicarboxylate (3a) in moderate yield (Table 1). In the presence of tetrabutylammonium bromide (TBAB), the reaction in acetonitrile afforded product 3a in 85% yield. The reaction in DCM gave the product 3a in 65% yield. However, no product 3a was obtained when the reaction was carried out in toluene at room temperature or in acetonitrile at 0 °C. The yield of 3a remained the same when the reaction was carried out at elevated temperature. At last, using of higher loading of TBAB and prolonging the reaction time could not increase the yield of the product 3a. Therefore, the functionalized 5-hydroxy-cyclopent-1-ene derivatives can be conveniently prepared in satisfactory yield in very simple reaction conditions. It should be pointed that a similar triethylamine-promoted multicomponent reaction of phenacyl bromide, malononitrile, dialkyl but-2-yneedioate, and triphenylphosphine has been already reported, in which diethyl 3-phenyl-5,5-dicyanocyclopent-2-ene-1,2-dicarboxylates were produced by further elimination of a hydroxy group [30]. In the present reaction, the hydroxy group is still remained in the product 3a. This result might be due to the weak basic system and the milder
conditions. An attempt to develop a three-component reaction by directly using the phenacyl bromide and malononitrile to replace the previously prepared phenacylmalononitrile in the reaction was not successful. The reaction gave a very complex mixture of products.

### Table 1: Optimization of reaction conditions.

| Entry | Base   | Solvent | Temp. (°C) | Time (h) | Yield (%) |
|-------|--------|---------|------------|----------|-----------|
| 1     | K$_2$CO$_3$ | MeCN    | rt         | 12       | 50        |
| 2     | TBAC   | MeCN    | rt         | 12       | 35        |
| 3     | TBAB   | MeCN    | rt         | 12       | 85        |
| 4     | TBAB   | DCM     | rt         | 12       | –         |
| 5     | TBAB   | PhMe    | rt         | 12       | –         |
| 6     | TBAB   | MeCN    | 50         | 12       | 75        |
| 7     | TBAB   | MeCN    | 50         | 24       | 84        |

*Reaction conditions: p-methylphenacylmalononitrile (0.5 mmol), dialkyl but-2-ynedioate (0.6 mmol), base (0.25 mmol), solvent (5.0 mL). rt, 12 h. Isolated yields.*

Under the optimized reaction conditions (Table 1, entry 3), the scope of the reaction was investigated by using various substrates and the results are summarized in Table 2. It can be seen that all reactions proceeded smoothly to give the expected functionalized 5-hydroxycyclopentenes 3a–l in good to excellent yields. The phenacylmalononitriles with electron-donating groups usually gave higher yields than that of substrates bearing an electron-donating chloro, bromo and nitro group. Both diethyl and dimethyl but-2-ynedoates can be successfully employed in the reaction. Because there is only one chiral carbon atom in the molecule, there are no diastereoisomers in the obtained products 3a–l. The chemical structures of compounds 3a–l were fully characterized by IR, HRMS, $^1$H and $^{13}$C NMR spectra. As for an example, the $^1$H NMR spectrum of compound 3i displayed a singlet at 3.52 ppm for the hydroxy group and two singlets at 3.24, 3.96 ppm with $J = 14.8$ Hz for the two diastereotopic protons of the cyclic methylene unit. The single crystal structure of compound 3k was successfully determined by X-ray diffraction analysis (Figure 1). From Figure 1, it can be seen that the C–C double bond is connected to two methoxy-carbonyl groups. Though one hydroxy group exists on the reactive allyl position and benzyl position, it still is present in the molecule and did not give the cyclopentadiene by further elimination of water.

### Table 2: Synthesis of functionalized cyclopentenes 3a–l.

| Entry | Product | Ar     | R    | Yield (%) |
|-------|---------|--------|------|-----------|
| 1     | 3a      | $p$-CH$_3$C$_6$H$_4$ | Et   | 85        |
| 2     | 3b      | C$_6$H$_5$ |      | 75        |
| 3     | 3c      | $m$-CH$_3$C$_6$H$_4$ | Et   | 73        |
| 4     | 3d      | $p$-CH$_3$OC$_6$H$_4$ | Et   | 88        |
| 5     | 3e      | o-CH$_3$OC$_6$H$_4$ | Et   | 62        |
| 6     | 3f      | $p$-ClC$_6$H$_4$ | Et   | 60        |
| 7     | 3g      | $p$-BrC$_6$H$_4$ | Et   | 62        |
| 8     | 3h      | $p$-NO$_2$C$_6$H$_4$ | Et   | 56        |
| 9     | 3i      | $p$-CH$_3$C$_6$H$_4$ | Me   | 78        |
| 10    | 3j      | $p$-CH$_3$OC$_6$H$_4$ | Me   | 80        |
| 11    | 3k      | $p$-ClC$_6$H$_4$ | Me   | 52        |
| 12    | 3l      | $p$-BrC$_6$H$_4$ | Me   | 55        |

*Reaction conditions: phenacylmalononitrile (0.5 mmol), dialkyl but-2-ynedioate (0.6 mmol), TBAB (0.25 mmol), CH$_3$CN (5.0 mL). rt, 12 h. Isolated yields.*

In order to obtain the corresponding products with elimination of water, alternative conditions for the base-promoted reaction of phenacylmalononitrile and dialkyl but-2-ynedoates were tested. After carefully examining the reaction conditions, we found that the reaction of phenacylmalononitriles and dialkyl but-2-ynedoates in acetonitrile at room temperature gave the unexpected products 4a–l in moderate to good yields in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as base promoter and the results are summarized in Table 3. It can be
Figure 2: Single crystal structure of compound 4a.
Figure 3: Single crystal structure of compound 4c.

Scheme 2: Proposed reaction mechanism for compounds 3, 4, and 5.
final product 3 by the protonation of the species C. The protonated species 5 could be successfully isolated in 12% yield after six hours when the reaction was carried out in weak basic solution (Supporting Information File 1) and its single crystal structure was determined by X-ray diffraction (Figure 4). When DABCO was used as a base, the further addition of the alkoxide ion to the cyano group in cis-position of the cyclopentyl ring produced a bridged cyclic 2-oxabicyclo[2.2.1]hept-5-ene D. The further hydration of intermediate D gave intermediate E, which was in turn transferred to cyclopentenyl intermediate F by the ring opening of the bridge ring. In the cyclopentenyl intermediate F, the hydroxy group and the amide group clearly exist in cis-position. Sequentially, nucleophilic addition of the amino group of intermediate F to the C–C double bond connecting the two alkoxy carbonyl groups in molecule 3 resulted in the formation of intermediate G. At last, the base-catalyzed dehydration and elimination of hydrocyanide gave the final product 4. It is due to the in situ formation and ring-opening of 2-oxabicyclo[2.2.1]hept-5-ene, that only one diastereoisomer 4 with the aryl group and the remaining cyano group in cis-position was selectively formed in the domino reaction process.

In order to shed light on the proposed reaction mechanism, some control experiments were carried out. After finishing the reaction of phenacylmalononitrile and diethyl but-2-ynedioate in the presence of TBAB under the standard reaction conditions, DABCO was directly added to the reaction system (Scheme 3). The further reaction at room temperature for 24 hours afforded the expected product 4d in 45% yield. This result clearly showed that the initially formed functionalized cyclopentene 3b could be smoothly transferred to the carboxamide-bridged dicyclopentene 4d, which also strongly supported the above proposed reaction mechanism.

**Conclusion**

In summary, we have investigated the cycloaddition of phenacylmalononitriles and dialkyl but-2-yne diodes under different reaction conditions and identified convenient synthetic protocols for the synthesis of functionalized cyclopent-2-ene and complex dicyclopentene derivatives in satisfactory yields. The stereochemistry of the reactions was clearly elucidated and a rational reaction mechanism was proposed. The reactions have the advantages of using readily available reagents, mild reaction conditions, good yields, and high diastereoselectivity,
and have potential synthetic applications in organic and medicinal chemistry.

**Experimental**

1. **General procedure for the preparation of functionalized cyclopent-2-enes 3a–l:** To a round-bottomed flask was added phenacylmalononitrile (0.5 mmol), dialkyl but-2-ynedioate (0.6 mmol), tetrabutylammonium bromide (0.25 mmol), and acetonitrile (5.0 mL). The solution was stirred at room temperature for twelve hours. After removing the solvent by rotary evaporation at reduced pressure, the residue was subjected to column chromatography with a mixture of ethyl acetate, petroleum ether and methylene dichloride 1:9:3 (v/v/v) as eluent to give the pure product for analysis.

2. **General procedure for the preparation of functionalized carboxamide-bridged dicyclopentenes 4a–k:** To a round-bottomed flask was added phenacylmalononitrile (0.5 mmol), dialkyl but-2-ynedioate (0.6 mmol), DABCO (1.0 mmol), and acetonitrile (5.0 mL). The solution was stirred at room temperature for 24 hours. After removing the solvent by rotary evaporation at reduced pressure, the residue was subjected to column chromatography with a mixture of ethyl acetate, petroleum ether and methylene dichloride 1:9:3 (v/v/v) as eluent to give the pure product for analysis.

**Diethyl 3,3-dicyano-5-hydroxy-5-((p-tolyl)cyclopent-1-ene-1,2-dicarboxylate (3a):** white solid, 85%; mp 151–153 °C; 1H NMR (400 MHz, CDCl₃) δ 7.29–7.27 (m, 2H, ArH), 7.21–7.20 (m, 2H, ArH), 4.47–4.41 (m, 2H, OCH₂), 4.21–4.17 (m, 2H, OCH₂), 3.52 (s, 1H, OH), 3.23 (d, J = 14.4 Hz, 1H, CH₂), 2.96 (d, J = 14.4 Hz, 1H, CH₂), 2.36 (m, 2H, CH₂), 1.41 (t, J = 6.8 Hz, 3H, CH₃), 1.14 (t, J = 6.8 Hz, 3H, CH₃); 13C NMR (100 MHz, CDCl₃) δ 163.2, 159.2, 152.7, 139.0, 138.1, 136.8, 129.6, 129.5, 124.7, 113.5, 113.5, 86.9, 63.2, 62.7, 52.3, 38.1, 21.1, 13.9, 13.7; HRMS–ESI (m/z): [M + Na⁺] calcd for C₂₀H₂₀Na₂O₅, 391.1270; found, 391.1271.

**Diethyl 3-cyano-1-(1-cyano-2,3-bis(ethoxycarbonyl)-4-tolyl)cyclopent-1-ene-1,2-dicarboxylate (4a):** yellow solid, 62%; mp 182–184 °C; 1H NMR (400 MHz, CDCl₃) δ 8.92 (s, 1H, NH), 7.46 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 6.90 (s, 1H, CH, 6.88–6.84 (m, 4H, ArH), 4.62 (s, 1H, OH), 4.35–4.30 (m, 2H, OCH₂), 4.27–4.19 (m, 3H, OCH₂), 4.13–4.03 (m, 3H, OCH₂), 3.81 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.27 (d, J = 14.8 Hz, 1H, CH₂), 2.47 (d, J = 14.8 Hz, 1H, CH₂), 1.39 (t, J = 7.2 Hz, 3H, CH₃), 1.28 (t, J = 7.2 Hz, 3H, CH₃), 1.15 (t, J = 7.2 Hz, 3H, CH₃), 1.06 (t, J = 7.2 Hz, 3H, CH₃); 13C NMR (100 MHz, CDCl₃) δ 166.5, 164.2, 163.4, 161.1, 160.4, 159.5, 159.4, 153.7, 150.8, 142.6, 131.8, 129.9, 127.8, 126.9, 125.9, 124.8, 122.9, 117.5, 114.7, 113.6, 113.4, 86.0, 72.7, 64.3, 62.5, 62.0, 61.8, 55.4, 55.3, 52.9, 51.4, 13.9, 13.8, 13.7, 13.6; HRMS–ESI (m/z): [M + Na⁺] calcd for C₅₂H₃₉Na₂O₁₂, 764.2431; found, 764.2413.

**Supporting Information**

The crystallographic data of the compounds 3k (CCDC 2176733), 4a (CCDC 2176734), 4b (CCDC 2176735), and 5 (CCDC 2176736) have been deposited at the Cambridge Crystallographic Database Center (http://www.ccdc.cam.ac.uk).

**Supporting Information File 1**

Characterization data and 1H NMR, 13C NMR, and HRMS spectra of the compounds.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-99-S1.pdf]

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