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Base-catalyzed bicyclization of dialkyl glutaconates with cinnamoylacetamides: a synthetic strategy for isoquinolinedione derivatives†

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We report here that polysubstituted dihydroisoquinolones and isoquinolones can be constructed by the one-pot reaction of the readily available acyclic α,β-unsaturated carbonyl precursors and dialkyl glutaconates under mild basic conditions (1–45 min for the former *vs.* 1–6 h for the latter) *via* the domino process involving [3+3] annulation/intramolecular aza-cyclization.

The isoquinolone skeleton is a basic structural feature found in many natural and biologically active products, including the alternarlactam, pancratistatin, aromathecin alkaloids and (*Z*)-6-bromo-4-((4-(pyrrolidin-1-ylmethyl)phenylamino)methylene)isoquinoline-1,3-dione (Fig. 1).[1] These compounds possess diverse pharmacological and biological properties as well as structural complexity[1,2] and have attracted considerable attention from organic and medicinal chemists. For the construction of the isoquinolone framework, the condensation/cyclization routes,[3] transition-metal-catalyzed coupling annulations,[4] aza-Wackertype reactions,[5] Pomeranz–Fritsch reactions,[6] denitrogenative[7] and decarbonylative[8] cycloadditions, transition-metal-catalyzed oxidative annulation of benzamides with alkynes[9] or olefins,[10] *etc.*,[11] have been reported, in which an aromatic substrate is generally required. On the other hand, although several procedures using the acyclic precursors have been developed,[12] they suffer from the limited substrate scope, the lack of readily available precursors, tedious synthetic procedures or harsh reaction conditions. Thus, the direct and convenient synthesis of isoquinolone derivatives from easily available acyclic starting materials in a single step under very mild conditions remains a formidable challenge.

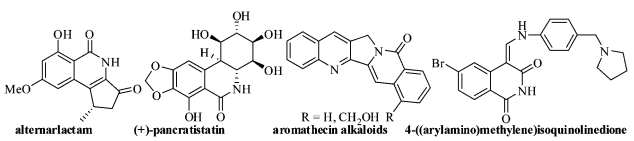
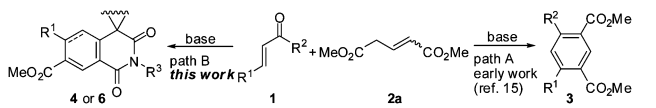


Fig. 1 Selected examples of biologically active and natural products containing the isoquinolone skeleton.

Domino reactions are attractive in industry and research laboratories because of their potential to save solvents, reagents, time and energy.[13] In our recent research to develop new domino reactions based on various easily available vinyl ketone precursors,[14] polysubstituted benzenes were prepared through a base-catalyzed [3+3] aerobic oxidative benzannulation of α,β-unsaturated carbonyl compounds **1** with dimethyl glutaconate **2a** (Scheme 1, path A).[15] On the basis of the above results, we envisioned that compounds containing the isoquinoline core, such as dihydroisoquinoline-1,3-diones **4** and isoquinoline-1,3-diones **6**, could be constructed through a domino reaction involving an initial intermolecular [3+3] annulation of α,β-unsaturated carbonyl compounds **1** with dimethyl glutaconate **2a**, followed by an intramolecular aza-cyclization/aromatization process under basic conditions if suitable acetamide groups were inserted at the α′-position of α,β-unsaturated carbonyl compounds **1** (path B). Compared with the approaches mentioned above,[3–12] the new method has the advantages of employing readily available starting materials and cheap reagents, as well as providing good regioselectivities without the requirement of metal catalysts. Herein, the preliminary results are described.

In the present study, initially, the model reaction of *N*-aryl-cinnamoylacetamide **1a** with dimethyl glutaconate **2a** was examined carefully to optimize the reaction conditions (Table 1). Indeed, the desired 5,6-dihydroisoquinoline-1,3-dione **4a** could be obtained in high yields when **1a** (0.5 mmol) was treated with **2a** (1.0 mmol) in MeOH (4.0 mL) in the presence of NaOH (0.10 mmol), *t*-BuOK (0.10 mmol) or DBU (0.10 mmol; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) at room temperature for 18 min (entries 3, 6 and 7).[16] Further



Scheme 1 Cyclization strategy of α,β-unsaturated carbonyl compounds with dimethyl glutaconate.

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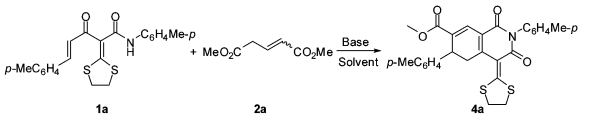
Table 1 Optimization of reaction conditions



1a 2a 4a

Entry	Base (equiv.)	**2a** (equiv.)	Solvent	*t*/h	**4a**[a] (%)
1	NaOH (0.1)	2.0	MeOH	24	35
2	NaOH (0.2)	1.0	MeOH	1	74
3	***NaOH (0.2)***	***2.0***	***MeOH***	***0.3***	***86***
4	NaOH (0.2)	2.5	MeOH	0.3	81
5	NaOH (0.5)	2.0	MeOH	0.3	84
6	DBU (0.2)	2.0	MeOH	0.3	86
7	*t*-BuOK (0.2)	2.0	MeOH	0.3	83
8	K_2CO_3 (0.2)	2.0	MeOH	0.5	76
9	DABCO (0.2)	2.0	MeOH	24	51
10	NaOH (0.2)	2.0	CH_3CN	3	61
11	NaOH (0.2)	2.0	THF	5	30
12	NaOH (0.2)	2.0	DMF	5	0

[a] Isolated yield.

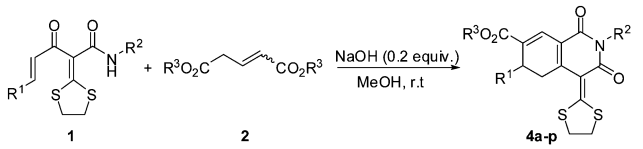
increasing the amounts of NaOH and **2a** did not improve the yield of **4a** (entries 4 and 5). Other bases, such as K_2CO_3 and 1,4-diazabicyclo[2.2.2]octane (DABCO), were less effective (entries 8 and 9). Among the solvents tested, methanol seemed to be the best choice. Other solvents, such as CH_3CN and THF, gave lower product yields (entries 10 and 11). No desired **4a** could be detected when the reaction was carried out in DMF (entry 12).

Next, the scope of the reaction was investigated under the optimal conditions, described in Table 1, entry 3, and the results are summarized in Table 2. It was found that the tandem reaction showed broad tolerance for various R^1 and R^2 groups of substrates **1**. All selected substrates, **1a–e** bearing phenyl (entry 2), electron-deficient (entry 3), electron-rich aryl (entry 1) and heteroaryl (entries 4 and 5) R^1 groups, reacted smoothly with dimethyl glutaconate **2a** to give the corresponding polysubstituted 5,6-dihydroisoquinoline-1,3-diones **4a–e** in high yields at room temperature for 18–30 min. Similarly, the reaction of substrate **1f** bearing a phenylvinyl R^1 group can give the desired **4f** in 70% yield (entry 6). On the other hand, various aromatic and benzyl R^2 groups at the nitrogen of **1** are also well-tolerated in the reaction and the corresponding polysubstituted 5,6-dihydroisoquinoline-1,3-diones **4a–o** were prepared in high yields (entries 1–15). In addition, in the case of diethyl glutaconate **2b**, the bicyclization reaction also worked well, yielding the desired product **4p** in 80% yield (entry 16).

To test the generality of this new approach for the construction of the dihydroisoquinolone core, the reactions of dimethyl glutaconate **2a** with selected 1-cinnamoylcyclopropanecarboxamides **5a–g** were examined under identical conditions as above. Fortunately, polysubstituted 5,6-dihydroisoquinoline-1,3-diones **4q–w** can also be prepared in good to high yields, respectively (Table 3, entries 1–7).

On the basis of the above experimental results together with the consideration of the structural feature of dihydroisoquinolones **4**, we reasoned that the isoquinolones **6** can be prepared from cinnamoylacetamides **1** or **5** and dimethyl glutaconate **2a** following a sequential intermolecular [3+3] annulation, intramolecular aza-cyclization and aromatization procedure in a single step under suitable reaction conditions, respectively. Detailed examination of the reaction conditions indicated that the isoquinoline-1,3-dione **6a** could be obtained in 90% yield from **1a** (0.5 mmol) and **2a** (1.0 mmol) in MeOH (4.0 mL) in the presence of NaOH (0.25 mmol) at 60 °C for 4 h in open air (Scheme 2). Similarly, the corresponding polysubstituted isoquinoline-1,3-diones **6b–g** were synthesized in high yields from reactions of **2a** with **1b**, **1c**, **1f**, **1l**, **1p** and **1q**, respectively (Scheme 2). Notably, the isoquinoline-1,3-diones **6h** and **6i** could be prepared in 75% and 65% yields at room temperature for 6 h under otherwise identical conditions as above (Scheme 2). In addition, in the case of the reactions of 1-cinnamoylcyclopropanecarboxamides **5d–f** with **2a**, the cyclization–aromatization reaction could also proceed at room temperature for 1 h to give the corresponding isoquinoline-1,3-diones **6j–l** in high yields under otherwise identical conditions as above (Scheme 2). The above reaction not only provides a facile and efficient access to isoquinolones in a single step from easily available acyclic starting materials under mild conditions, but also offers further enhancement of the efficiency of the bicyclization strategy.

Table 2 Synthesis of 5,6-dihydroisoquinoline-1,3-diones **4a–p**[a]

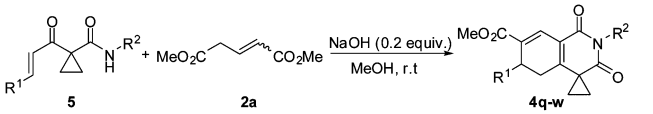


1 2 4a-p

Entry	**1**	R^1	R^2	R^3	*t*/min	Yield[b] (%)
1	**1a**	4-MeC_6H_4	4-MeC_6H_4	Me	18	**4a** (85)
2	**1b**	C_6H_5	4-MeC_6H_4	Me	20	**4b** (74)
3	**1c**	4-ClC_6H_4	4-MeC_6H_4	Me	20	**4c** (82)
4	**1d**	2-Furyl	4-MeC_6H_4	Me	30	**4d** (75)
5	**1e**	2-Thienyl	4-MeC_6H_4	Me	30	**4e** (74)
6	**1f**	PhCH=CH	4-MeC_6H_4	Me	18	**4f** (70)
7	**1g**	4-ClC_6H_4	4-ClC_6H_4	Me	30	**4g** (84)
8	**1h**	C_6H_5	4-ClC_6H_4	Me	25	**4h** (84)
9	**1i**	4-ClC_6H_4	C_6H_5	Me	25	**4i** (80)
10	**1j**	4-MeC_6H_4	C_6H_5	Me	30	**4j** (73)
11	**1k**	C_6H_5	C_6H_5	Me	25	**4k** (82)
12	**1l**	4-ClC_6H_4	$CH_2C_6H_5$	Me	20	**4l** (81)
13	**1m**	4-MeC_6H_4	$CH_2C_6H_5$	Me	20	**4m** (74)
14	**1n**	C_6H_5	$CH_2C_6H_5$	Me	20	**4n** (76)
15	**1o**	4-ClC_6H_4	2,4-MeC_6H_3	Me	20	**4o** (76)
16	**1b**	C_6H_5	4-MeC_6H_4	Et	45	**4p** (80)

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), NaOH (0.10 mmol), MeOH (4.0 mL), room temperature for 18–45 min. [b] Isolated yield.

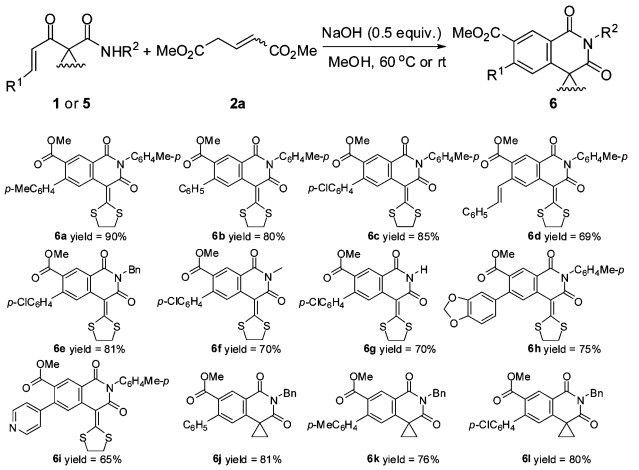
Table 3 Synthesis of 5,6-dihydroisoquinoline-1,3-diones **4q–w**[a]



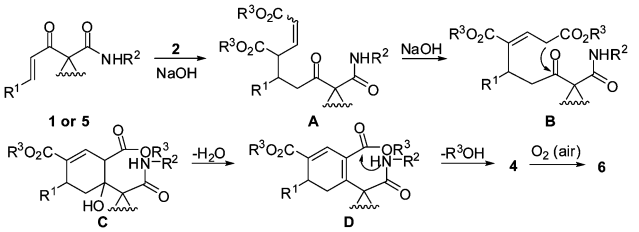
5 2a 4q-w

Entry	**5**	R^1	R^2	*t*/min	Product	Yield[b] (%)
1	**5a**	4-ClC_6H_4	4-$MeOC_6H_4$	20	**4q**	75
2	**5b**	4-MeC_6H_4	4-$MeOC_6H_4$	40	**4r**	55
3	**5c**	C_6H_5	4-$MeOC_6H_4$	20	**4s**	58
4[c]	**5d**	C_6H_5	Bn	1	**4t**	81
5[c]	**5e**	4-MeC_6H_4	Bn	1	**4u**	83
6[c]	**5f**	4-ClC_6H_4	Bn	1	**4v**	77
7[c]	**5g**	2-Thienyl	Bn	1	**4w**	84

[a] Reaction conditions: **5** (0.5 mmol), **2a** (1.0 mmol), NaOH (0.10 mmol), MeOH (4.0 mL), room temperature for 1–40 min. [b] Isolated yield. [c] A trace amount of isoquinolone **6** was observed by TLC.



Scheme 2 Synthesis of polysubstituted isoquinoline-1,3-diones **6**.



Scheme 3 Proposed mechanism for formation of **4** and **6**.

On the basis of the above experimental results together with related reports,[15,17] a possible mechanism for the formation of isoquinolones **4** and **6** is proposed in Scheme 3. In the presence of NaOH, the reaction starts from the intermolecular Michael addition of **2** to **1** or **5** to give intermediate **A.** Subsequently, the intermediate **B,** generated *via* C=C double bond isomerization of intermediate **A** under basic conditions, undergoes an intramolecular aldol cyclization, followed by dehydration to afford the six-membered intermediate **D.** Finally, the nitrogen atom of intermediate **D** attacks the carbonyl carbon under basic conditions and leads to an intramolecular aza-cyclization to produce the 5,6-dihydroisoquinoline-1,3-dione **4,** which undergoes an oxidative aromatization with molecular oxygen (from air) to give the isoquinoline-1,3-dione **6** (Scheme 3).

In conclusion, we have developed a new domino strategy for the rapid and efficient synthesis of polysubstituted dihydroisoquinolone and isoquinolone derivatives. The reaction involves a sequential intermolecular [3+3] annulation/intramolecular aza-cyclization procedure and allows the construction of 5,6-dihydroisoquinoline-1,3-diones and isoquinoline-1,3-diones in a single step from the easily available acyclic substrates in good to high yields under mild metal-free conditions. This strategy shows the highly efficient use of the reactive sites of substrates and further expands the synthetic potential of dialkyl glutaconates in organic synthesis. Further studies are in progress.

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