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Organocatalyzed synthesis of 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles

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ABSTRACT

2-Amino-8-oxo-tetrahydro-4*H*-chromene-3-carbonitriles were synthesized for the first time from a tandem Michael addition-cyclization reaction between cyclohexane-1,2-dione and benzylidenemalononitriles. An enantioselective synthesis of these compounds was achieved in moderate ee values (up to 63% ee) by using a cinchona alkaloid-derived thiourea catalyst.

Polysubstituted 2-amino-4*H*-pyran-3-carbonitrile derivatives are very important heterocyclic compounds, which frequently exhibit a variety of biological activities.[1,2] Among these compounds, 2-amino-4*H*-chromene-3-carbonitrile derivatives have been reported to possess anticancer, anticoagulant, and fungicidal activities.[2] These compounds also find applications as pigments and as potential biodegradable agrochemicals.[3] Due to their usefulness, the synthesis of these compounds has attracted a lot of interest.[4] Most recently, asymmetric syntheses of some of these 2-amino-4*H*-pyran-3-carbonitrile derivatives have also been reported.[5] Furthermore, the synthesis of partially saturated 2-amino-4*H*-chromene-3-carbonitrile derivatives has also been reported.[6] For example, the cyclization reaction between 1,3-dicarbonyl compounds and benzylidenemalononitriles in the presence of a suitable base gives 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles,[6] which have also been demonstrated to have biological activities.[6a] Nonetheless, the synthesis of their 8-oxo analogues has not been reported, although such compounds reportedly are able to alter the lifespan of eukaryotic organisms.[7]

On the other hand, 1,2-diones are highly reactive compounds and have found many applications in organic synthesis.[8] Nevertheless, they have been seldom used in organocatalyzed reactions.[9] These few examples are collected below: Göbel and coworkers utilize the dione as an ene-activator in an organocatalyzed Diels–Alder reaction.[9a] Nair et al. reported a lactonization reaction between 1,2-diones and α,β-unsaturated aldehydes catalyzed by an *N*-heterocyclic carbene.[9b] In 2006, we reported a direct cross aldol reaction of 1,2-diones and ketones catalyzed by proline derivatives.[9c] Most recently, Rueping and coworkers reported a tandem[5,10] Michael-aldol reaction of cyclohexane-1,2-dione and α,β-unsaturated aldehydes.[9d]

We are interested in developing novel enantioselective methods for the synthesis of 2-amino-4*H*-pyran-3-carbonitrile derivatives. In this regard, we developed the first enantioselective synthesis of 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles through a tandem Michael addition-cyclization reaction between 2-pyrazolin-5-ones and benzylidenemalononitriles.[5b] The fact that cyclohexane-1,2-dione may be enolized and used in a Michael addition reaction under organocatalysis[9d] prompted us to use this compound as a potential Michael donor in a tandem Michael addition-cyclization reaction with benzylidenemalononitriles. Herein we wish to report the first general and enantioselective synthesis of 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles on the basis of a tandem Michael addition-cyclization reaction between benzylidenemalononitriles and cyclohexane-1,2-dione.

Cyclohexane-1,2-dione (**1**) and benzylidenemalononitrile (**2a**) were adopted as the starting materials for the proposed Michael addition reaction. On the basis of Rueping's results, the reaction was studied with several readily available organic and inorganic bases as the catalysts. The results are summarized in Table 1.

As shown in Table 1, when the reaction was carried out with 10 mol % DABCO as the base catalyst in toluene at room temperature for 27 h (entry 1), a product, which was identified to be **3a**,

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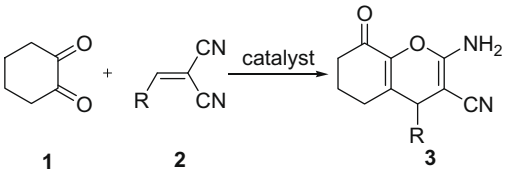
Table 1
Tandem Michael addition-cyclization reaction between 1,2-cyclohexanedione (**1**) and benzylidenemalononitriles (**2**)[a]

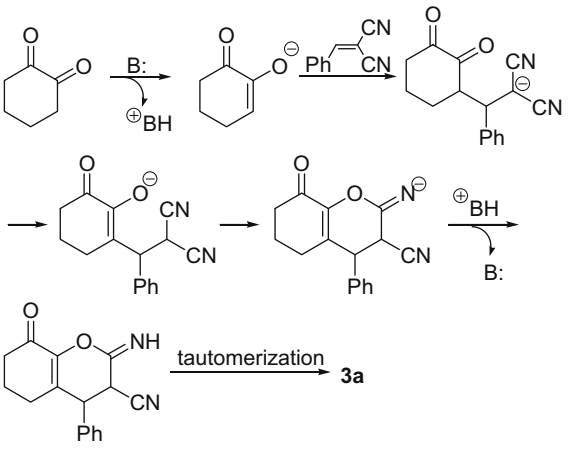


Entry	R	2/3	Solvent	Catalyst	Time (h)	Yield[b] (%)
1	Ph	**a**	Toluene	DABCO	27	75
2	Ph	**a**	Toluene	DBU	30	43
3	Ph	**a**	Toluene	Et_3N	38	67
4	Ph	**a**	Toluene	K_2CO_3	48	29
5	Ph	**a**	Toluene	$NaHCO_3$	72	0
6	Ph	**a**	CH_2Cl_2	DABCO	24	71
7	Ph	**a**	THF	DABCO	28	74
8	Ph	**a**	EtOAc	DABCO	27	64
9	Ph	**a**	Acetone	DABCO	29	51
10	Ph	**a**	EtOH	DABCO	30	61
11	4-ClC_6H_4	**b**	Toluene	DABCO	24	73
12	4-BrC_6H_4	**c**	Toluene	DABCO	30	59
13	4-CNC_6H_4	**d**	Toluene	DABCO	23	45
14	4-$NO_2C_6H_4$	**e**	Toluene	DABCO	22	64
15	3-BrC_6H_4	**f**	Toluene	DABCO	20	65
16	4-$CH_3C_6H_4$	**g**	Toluene	DABCO	25	67
17	Thiophen-2-yl	**h**	Toluene	DABCO	26	79
18	$CH_3(CH_2)_5$	**i**	Toluene	DABCO	32	39

[a] All reactions were conducted with the indicated arylidenemalononitrile (**2**, 0.30 mmol), 1,2-cyclohexanedione (**1**, 0.32 mmol), and the catalyst (10 mmol %, 0.03 mmol) in the specified solvent (1.5 mL) at room temperature.
[b] Yield of isolated product after column chromatography.

was isolated in 75% yield. Unlike Rueping's results,[9d] no formation of bridged bicyclic products was observed.[11] Formation of **3a** may be rationalized by the tandem enolization–Michael addition–enolization–cyclization reaction–tautomerization sequence as shown in Scheme 1. DBU, Et_3N, and K_2CO_3 also catalyze this reaction (entries 2–4), albeit in lower efficiency. However, a weaker base $NaHCO_3$ cannot catalyze the reaction, as no product could be obtained (entry 5). Further screening of the reaction solvents identified that toluene (entry 1), CH_2Cl_2 (entry 6), and THF (entry 7) are good solvents for this reaction, while EtOAc, acetone, and EtOH (entries 8–10) are worse ones. Under the optimized conditions, several substituted benzylidenemalononitriles were applied as the substrate. As shown by the results in Table 1, acceptable to good yields (45–73%) were obtained with benzylidenemalononitriles with an electron-withdrawing group substituted at the *para* position (entries 11–14). Benzylidenemalononitriles with a *meta* substituent (entry 15) or an electron-donating group (entry 16) also led to good results. Heterocyclic thiophen-2-ylmethylidenemalononitrile gave the highest yield of 79% of the desired product (entry 17). Alkylidenemalononitrile **2i** also reacted to produce the expected product **3i**, although the yield is lower and the reaction is sluggish (entry 18). However, other 1,2-diones, such as butane-2,3-dione and 3-methylcyclopentane-1,2-dione, do not yield the expected product (data not shown), with the former giving no product at all and the latter some unidentified products.

Since one stereogenic center is created at the 4-position of product **3** during this reaction, it was our intention to develop an asymmetric version of this reaction by using chiral Lewis base organocatalysts. Thus, with **1** and **2a** as the model substrates, several readily available chiral Lewis base organocatalysts (Fig. 1) were screened. The results of this screening are collected in Table 2. As detailed in Table 2, out of the 10 catalyst screened, only the quinine-derived thiourea catalysts **4a**, **4b**, and **4c** are giving slightly higher ee values (about 35% ee) when they were applied in toluene at room temperature (entries 1–3), while the rest all generated ee values no greater than 30% (entries 4–10). It should be pointed out that catalysts **4d**, **4e**, **4f**, **4g**, and **4j** (entries 4–7, and 10) produce the other enantiomer as the major product as compared to the rest catalysts. Because catalyst **4a** yields the best yields and the highest ee values among the three best catalysts, further optimizations were



Scheme 1. Proposed mechanism for the formation of product **3**.

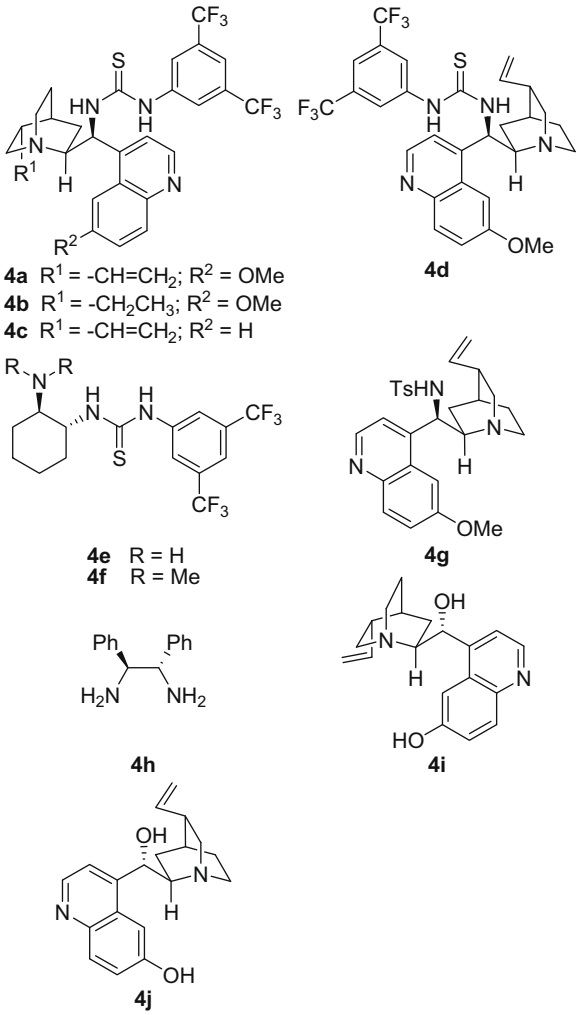
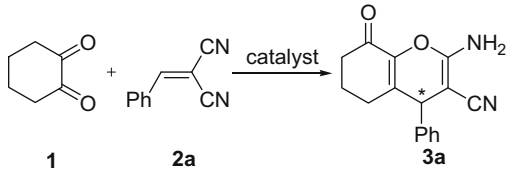


Figure 1. Chiral catalyst screened for the enantioselective synthesis of **3a**.

Table 2
Catalyst screening for the enantioselective synthesis of **3a**[a]

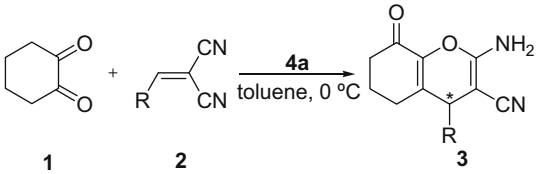


1 **2a** **3a**

Entry	Solvent	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	**4a**	26	56	35
2	Toluene	**4b**	30	41	35
3	Toluene	**4c**	30	47	34
4	Toluene	**4d**	28	37	30[d]
5	Toluene	**4e**	240	21	1[d]
6	Toluene	**4f**	40	34	27[d]
7	Toluene	**4g**	26	70	25[d]
8	Toluene	**4h**	168	31	3
9	Toluene	**4i**	28	61	16
10	Toluene	**4j**	28	72	3[d]
11	CH_2Cl_2	**4a**	30	43	18
12	Et_2O	**4a**	28	55	17
13	EtOAc	**4a**	28	35	25
14	THF	**4a**	40	33	33
15	$CHCl_3$	**4a**	38	33	6
16	CH_3CN	**4a**	28	31	15
17	EtOH	**4a**	28	53	40
18[e]	EtOH	**4a**	72	58	40
19[e]	Toluene	**4a**	28	64	63
20[f]	Toluene	**4a**	28	43	59

[a] Unless otherwise indicated, all reactions were conducted with benzylidenemalononitrile **2a** (0.30 mmol), cyclohexane-1,2-dione (0.32 mmol), and the catalyst (10 mmol %, 0.030 mmol) in the specified solvent (1.5 mL) at room temperature.
[b] Yield of isolated product after column chromatography.
[c] Determined by HPLC analysis on a ChiralCel OD-H column.
[d] The opposite enantiomer was obtained as the major product in these cases.
[e] The reaction was conducted at 0 °C.
[f] The reaction was conducted at −15 °C.

Table 3
Enantioselective synthesis of 2-amino-8-oxo-tetrahydro-4*H*-chromene-3-carbonitriles[a]



1 **2** **3**

Entry	R	**3**	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph	**3a**	28	64	63
2	4-ClC_6H_4	**3b**	24	60	58
3	4-BrC_6H_4	**3c**	30	55	57
4	4-CNC_6H_4	**3d**	24	51	43
5	4-$NO_2C_6H_4$	**3e**	26	55	48
6	3-BrC_6H_4	**3f**	24	63	52[d]
7	4-$CH_3C_6H_4$	**3g**	28	49	50
8	Thiophen-2-yl	**3h**	30	37	47[e]
9	$CH_3(CH_2)_5$	**3i**	96	12	9[d]

[a] All reactions were conducted with the benzylidenemalononitrile (0.30 mmol), cyclohexane-1,2-dione (0.32 mmol), and catalyst **4a** (10 mol %, 0.030 mmol) in toluene (1.5 mL) at 0 °C.
[b] Yield of isolated product after column chromatography.
[c] Unless otherwise specified, ee values were determined by HPLC analysis on a ChiralCel OD-H column.
[d] Determined by HPLC analysis on a ChiralPak AD-H column.
[e] Determined by HPLC analysis on a ChiralPak AS column.

focused on catalyst **4a**. Screening different organic solvents revealed that most of these solvents (entries 11–16) produce worse ee values of the product than toluene does (entry 1). Only in ethanol a higher ee value of 40% was achieved (entry 17). Nevertheless, the attempt to further increase the ee value through lowering the reaction temperature failed in this solvent, since at 0 °C the same ee value was obtained (entry 18). We then went back to toluene and tried to increase the ee value by employing the temperature effects. To our pleasure, with toluene, the ee value of the product **3a** may be increased to 63% at 0 °C (entry 19). However, further dropping of the temperature (to −15 °C) proves to have detrimental effects on both the reactivity and the enantioselectivity of this reaction (entry 20). Once the optimized reaction conditions were found, the other benzylidenemalononitriles were applied to this reaction under these conditions. The results are collected in Table 3.

As shown in Table 3, benzylidenemalononitriles with various substituents all produce the desired product in mediocre to good ee values (43–63% ee, entries 1–7). The yields (49–64%) obtained are usually low because of the formation of some unidentified products in the reaction. The heterocyclic thiophen-2-ylmethylidenemalononitrile also gives the expected product in 47% ee and 37% yield (entry 8). However, the alkylidenemalononitrile **2i** reacts very slowly and leads to a poor ee value of the product (entry 9). Again, butane-2,3-dione and 3-methylcyclopentane-1,2-dione failed to yield the desired products (data not shown).

In summary, we have developed the first general synthesis of 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles by employing a tandem Michael addition-cyclization reaction between cyclohexane-1,2-dione with benzylidenemalononitriles with DABCO as the catalyst. An enantioselective version of this reaction was also realized (with ee value up to 63%) by using a quinine-derived thiourea catalyst.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.139.

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11. The reaction does produce some unidentified products, which lowers the yield of the reaction.