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Domino reaction of arylaldehydes and 1-acetylcyclopropanecarboxamides: one-pot access to highly functionalized spiropiperidine-2,4-diones

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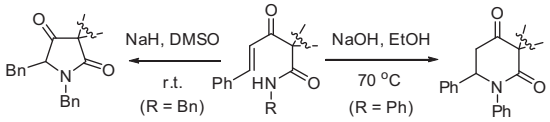
ABSTRACT

A domino reaction based on arylaldehydes and 1-acetylcyclopropanecarboxamides has been developed, which allows one-pot and efficient synthesis of structurally complex piperidine-2,4-diones with multiple functionalities under mild conditions. The overall transformation involves tandem aldol/intramolecular aza-Michael/(aldol)/Michael sequences.

Creation of molecular complexity and diversity[1] from simple substrates in an environmentally benign and atom-economic fashion[2] constitutes a great challenge in modern organic chemistry, both from academic and industrial points of view.[3,4] In these contexts, the development of domino reactions[5] have emerged as extremely powerful and popular. Domino processes allow multiple bond-forming events to occur in a single vessel and, as a consequence, significantly increase resource efficiency during the cascade.[5]

In our research on the syntheses of useful cyclic compounds via domino reactions,[6] the utilization of α,α-disubstituted β-ketoamides bearing both electrophilic and nucleophilic centers has been demonstrated in the construction of a variety of oxa- and aza-heterocycles including furoquinolines,[6a] furo[2,3-*b*]furans,[6b] spiroindan-2,2′-pyrrolidine,[6c] and fully functionalized pyridin-2(1*H*)-ones.[6d] More recently, the intramolecular Michael/anti-Michael addition reactions of *N*-aryl/alkyl-cinnamoylacetamides in relation to the remote electronic effect has been reported in our group (Scheme 1).[7] In conjunction with these studies and our continued interest regarding the synthetic potential of β-ketoamides,[8] we explored the aldol-initiated domino reaction of arylaldehydes **1** and β-ketoamides **2** containing carbonyl, carbamoyl, and cyclopropyl functionalities. As a result of the research, a one-pot domino reaction leading to highly substituted spiropiperidine-2,4-diones **3** were developed under mild conditions. Piperidine-2,4-diones, as typical six-membered nitrogen heterocycles, are important motifs in many biologically and pharmaceutically interesting compounds,[9] as well as useful intermediates in organic synthesis.[10] Although several approaches for the synthesis of this system have been presented, development of simple and convenient synthetic procedures for such nitrogen-containing heterocycles represents an attractive and interesting area of research in synthetic organic and medicinal chemistry.[11] Herein, we wish to report our recent results.

The substrates, 1-acetylcyclopropanecarboxamides **2**, were prepared following the procedure described in the literature.[6a] With substrates **2** in hand, optimization of the reaction conditions was conducted (Table 1). It was found that no matter at room temperature in *t*-BuOK/*t*-BuOH, NaOH/DMF, NaOH/CH_3CN, NaH/DMSO, or at 70 °C in NaOH/EtOH, the reactions of phenylaldehyde **1a** and 1-acetyl-*N*-phenylcyclopropanecarboxamide **2a** could not give satisfactory results (entries 1, 2, 4–6). However, to our delight, the model reaction between **1a** (1.1 mmol) and **2a** (1.0 mmol) could proceed efficiently with NaOH/EtOH at room temperature (entry 3). A white solid was obtained in 65% yield after workup and purification by column chromatography, which was characterized as 5-phenyl-5-azaspiro[2.5]octane-4,8-dione **3a** on



Scheme 1.

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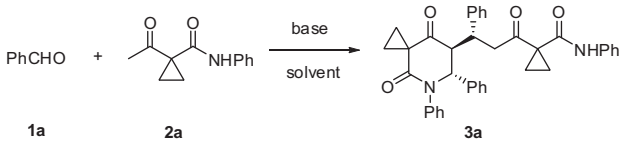
Table 1
Optimization of the reaction conditions of phenylaldehyde **1a** with 1-acetylcyclopropanecarboxamide **2a**[a]



1a 2a 3a

Entry	Base	Solvent	*T* (°C)	Time (h)	Yield (%)[b]
1	*t*-BuOK	*t*-BuOH	rt	12	No reaction
2	NaOH	DMF	rt	12	Trace
3	NaOH	EtOH	rt	5.5	65
4	NaOH	EtOH	70	8	0
5	NaOH	CH_3CN	rt	6	23
6	NaH	DMSO	rt	4.5	Complicated

[a] Reactions were carried out on a 1.0-mmol scale in 5.0 mL of solvent with **1a** (1.1 equiv), **2a** (1.0 equiv), and a base (1.0 equiv).
[b] Yield of isolated product.

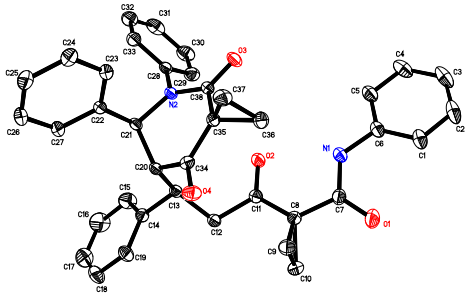
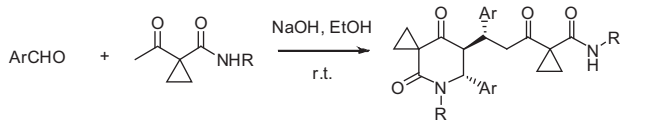


Figure 1. ORTEP drawing of **3a**.

the basis of its spectral and analytical data.[12] It was noteworthy that compound **3a** was formed in a diastereospecific manner based on its ^1H and ^{13}C NMR spectra. The structure of **3a** and its stereochemistry were further confirmed by the X-ray single crystal diffraction (Fig. 1).[13]

Having established optimal reaction conditions, we next examined the scope and limitation of the reactions based on arylaldehydes **1** and 1-acetylcyclopropanecarboxamides **2**.[14] First of all, a series of arylaldehydes **1** (1.1 mmol) were reacted with 1-acetyl-*N*-phenylcyclopropanecarboxamide **2a** (1.0 mmol) under the optimized conditions (EtOH/NaOH, rt) and some of the results are summarized in Table 2. Consequently, all the reactions with phenylaldehyde (entry 1), electron-rich arylaldehydes (entries 2–5), less electron-deficient arylaldehydes (entries 6–7), and heteroarylaldehyde (entry 8) proceeded smoothly to afford the corresponding highly functionalized spiropiperidine-2,4-diones **3a–h** in good yields (45–71%).[15] However, for strong electron-withdrawing arylaldehydes like 2-nitrobenzaldehyde and pyridine-4-carboxyaldehyde, the corresponding products **3** could not been obtained. Similar to the results reported, only the aldol condensation product **4** was separated in 95% yield for 2-nitrobenzaldehyde and the aldol/aza-anti-Michael addition product **5** was obtained in 82% yield for pyridine-4-carboxyaldehyde (Scheme 2).[7] Then the reaction scope with respect to the amide motif was examined. When the substituent on nitrogen was aryl, such as 4-MeOPh, 4-MePh, or 2-ClPh, the desired piperidine-2,4-diones **3i–k** were obtained in moderate yields of 46–65% (Table 1, entries 9–11).[16] As for *N*-alkyl substituted β-ketoamides like 1-acetyl-*N*-benzylcyclopropanecarboxamide **2e**, the reaction could not give the spiropiperidine-2,4-dione product (entry 12). It was found that products **3a–k** were produced in high efficiency and in a highly

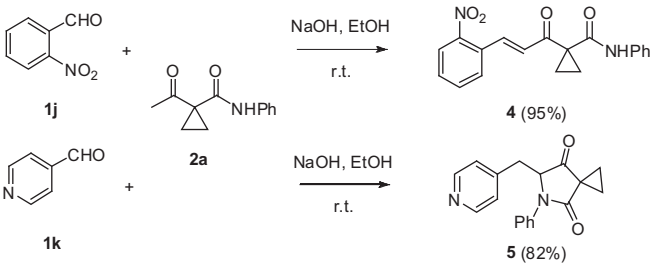
Table 2
Domino reactions of arylaldehydes with 1-acetylcyclopropanecarboxamides leading to spiropiperidine 2,4-diones **3**[a]



1 2 3

Entry	1	Ar	2	R	3[b] (Yield %)[c]
1	**1a**	C_6H_5	**2a**	C_6H_5	**3a** (65)
2	**1b**	2-$OMeC_6H_4$	**2a**	C_6H_5	**3b** (71)
3	**1c**	4-$OMeC_6H_4$	**2a**	C_6H_5	**3c** (56)
4	**1d**	3,4-$CH_2O_2C_6H_3$	**2a**	C_6H_5	**3d** (63)
5	**1e**	4-MeC_6H_4	**2a**	C_6H_5	**3e** (58)
6	**1f**	4-ClC_6H_4	**2a**	C_6H_5	**3f** (52)
7	**1g**	4-FC_6H_4	**2a**	C_6H_5	**3g** (45)
8	**1h**	2-Thienyl	**2a**	C_6H_5	**3h** (54)
9	**1a**	C_6H_5	**2b**	4-$MeOC_6H_4$	**3i** (65)
10	**1a**	C_6H_5	**2c**	4-MeC_6H_4	**3j** (52)
11	**1a**	C_6H_5	**2d**	2-ClC_6H_4	**3k** (46)
12	**1a**	C_6H_5	**2e**	Bn	**3l** (89)[d]

[a] Reactions were carried out on a 1.0-mmol scale in 5 mL of EtOH with **1** (1.1 equiv), **2** (1.0 equiv), and NaOH (1.0 equiv).
[b] The stereochemistry of **3** was assigned by the single crystal structure of **3a**.
[c] Yield of isolated product.
[d] Only the corresponding aldol condensation product was obtained.

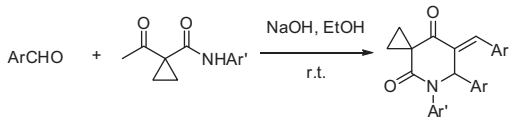


Scheme 2. Reactions of strong electron-withdrawing arylaldehydes with **2a**.

regio- and diastereoselective manner. In all cases, three adjacent stereocenters were created simultaneously and no diastereoisomers were observed. The procedures involve two molecular of **1** and two molecular of **2**, giving rise to complex structures with multiple functionalities, three continuous chiral carbon atoms and two separate cyclopropanes. In the domino process, up to four consecutive bonds including one C–N bond and three C–C bonds were established.

When excessive arylaldehydes were employed in the above-mentioned reactions, spiropiperidine-2,4-diones **6** would be obtained (Table 2). Specifically, upon treatment of **1a** (3.0 equiv) with **2b** (1.0 mmol) in the presence of NaOH (2.0 equiv) in EtOH (5 mL) at room temperature for 3 h, the reaction afforded 7-benzylidene-5,6-diphenyl-5-azaspiro[2.5]octane-4,8-dione **6a** in a moderate yield of 41% (Table 3, entry 1). Selected arylaldehydes **1** were reacted with 1-acetylcyclopropanecarboxamides **2** to give spiropiperidine-2,4-diones **6b–d** under otherwise identical conditions (entries 2–4). The structure of **6** was established based on the spectral and analytical data. It was noteworthy that the yields of products **6** were not fairly high, which was attributed to the formation of certain amount of compounds **3** in the reactions.[17] The one-pot reaction provides a direct and convenient route to spiro compound of type **6** with one cyclopropanyl ring, one chiral carbon atom, and an exocyclic double-bond. During this cascade, three consecutive bonds including one C–N bond and two C–C

Table 3
Domino reactions of arylaldehydes with 1-acetylcyclopropanecarboxamides leading to spiropiperidine 2,4-diones **6**[a]



1 2 6

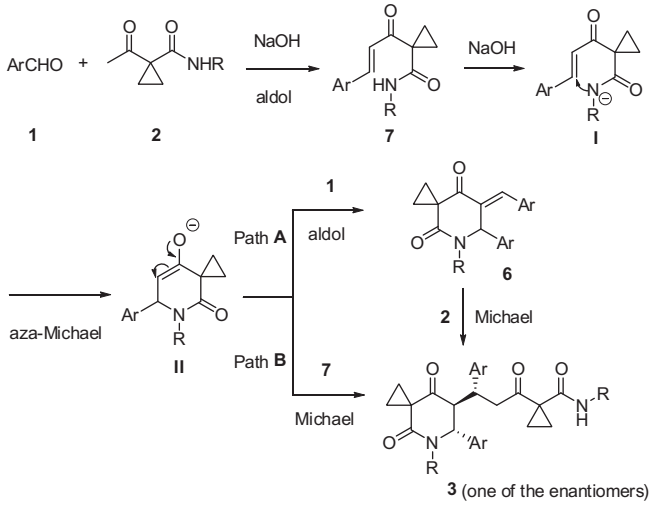
Entry	1	Ar	2	Ar′	6 (Yield %)[b,c]
1	**1a**	C_6H_5	**2b**	4-$MeOC_6H_4$	**6a** (41)
2	**1a**	C_6H_5	**2c**	4-MeC_6H_4	**6b** (35)
3	**1e**	4-MeC_6H_4	**2c**	4-MeC_6H_4	**6c** (38)
4	**1e**	4-MeC_6H_4	**2e**	4-ClC_6H_4	**6d** (44)

[a] Reactions were carried out on a 1.0-mmol scale in 5 mL of EtOH with **1** (3.0 equiv), **2** (1.0 equiv), and NaOH (2.0 equiv).
[b] Yield of isolated product.
[c] The formation of compounds **3** was observed on TLC.

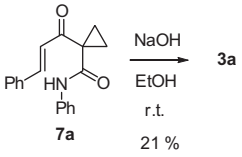
bonds were created. Indeed, spiro compounds **3** and **6** could be synthesized, respectively, with different mole ratio of reactants. The richness of the functionality on the piperidine-2,4-diones of types **3** and **6** may render them extremely versatile as synthons in further synthetic transformations.[18]

Based on all the results mentioned above, a possible mechanism for the highly efficient one-pot transformation into spiropiperidine-2,4-diones **3** was proposed, as depicted in Scheme 3. A tandem aldol condensation and intramolecular aza-Michael addition of arylaldehyde and β-ketoamides take place first, giving the key enolate intermediate **II** (**7** → **I** → **II**).[19] Then, the spiropiperidine-2,4-diones **3** would be produced via a second aldol condensation of **II** with **1** giving piperidine-2,4-diones **6** with an exocyclic double-bond and a second Michael addition between **6** and **2** (Path **A**).[20]

There is an alternative pathway to form spiro compounds **3**, that is, an intermolecular Michael addition between **II** and **7** (Path **B**), which can not be completely ruled out. In order to further elucidate the possible mechanism, the condensation product **7a** was subjected to the reactions under otherwise identical conditions (Eq. 1). Consequently, compound **3a** was obtained in ~21% yield. The observation supports the possibility of Path **B**, in which a tandem aldol/aza-Michael/Michael sequence was involved starting from the substrates **1** and **2**.



Scheme 3. Possible mechanism for the domino reactions leading to spiropiperidine-2,4-diones **3**.



(1)

In conclusion, a concise and efficient synthesis of fully functionalized piperidine-2,4-diones **3** and **6** has been developed based on the one-pot domino reaction of arylaldehydes and 1-acetylcyclopropanecarboxamides. The overall transformation involves tandem aldol/intramolecular aza-Michael/(aldol)/Michael sequences. This protocol is associated with readily available starting materials, mild conditions, dense and flexible substitution patterns, and potential synthetic utility of the final products.

Acknowledgments

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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.2010.09.133.

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13. CCDC 771686 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. Typical procedure for the preparation of **3** (**3a** as an example): To a solution of 1-acetylcyclopropanecarboxamide **2a** (203 mg, 1.0 mmol) in EtOH (5 mL) was added phenylaldehyde **1** (0.12 mL, 1.1 mmol) and NaOH (40 mg, 1.0 mmol). The mixture was stirred at room temperature. After the starting material **2a** was consumed as indicated by TLC, the reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether:diethyl ether = 4:1) to give **3a** (378 mg, 65%) as a white solid. 1-((*R*)-3-((6*R*,7*S*)-4,8-dioxo-5,6-diphenyl-5-azaspiro[2.5]octan-7-yl)-3-phenylpropanoyl)-*N*-phenylcyclopropanecarboxamide (**3a**): White solid. mp 188–190 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.27–1.32 (m, 1*H*), 1.54–1.58 (m, 1*H*) , 1.60–1.64 (m, 1*H*), 1.68–1.76 (m, 3*H*), 1.87–1.90 (m, 1*H*), 2.30–2.34 (m, 1*H*), 2.49–2.53 (m, 1*H*), 2.66–2.71 (m, 1*H*), 3.10–3.13 (m, 1*H*), 4.12 (t, *J* = 6.0 Hz, 1*H*), 4.64 (s, 1*H*), 7.05 (d, *J* = 7.5 Hz, 2*H*), 7.05–7.14 (m, 3*H*), 7.16–7.19 (m, 2*H*), 7.20–7.23 (m, 2*H*), 7.24–7.25 (m, 2*H*), 7.27–7.34 (m, 7*H*), 7.57 (d, *J* = 8.0 Hz, 2*H*), 10.80 (s, 1*H*). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 19.0, 19.7, 25.3, 26.0, 34.5, 34.9, 40.6, 42.1, 62.5, 63.1, 120.1, 124.1, 125.3, 125.7, 126.6, 127.9,128.0,128.1, 128.9, 128.9, 129.1, 129.4, 138.0,139.6, 140.4, 142.4, 166.7, 169.5, 206.5, 206.8. MS calcd *m*/*z* 582.2, found 583.2.2 $[(M+1)]^+$. Anal. Calcd for $C_{38}H_{34}N_2O_4$: C, 78.33; H, 5.88; N, 4.81; found: C, 78.30; H, 5.89; N, 4.79.
15. For synthetic details, see Supplementary data.
16. The yields corresponding to products **3** could not be further improved after several trials.
17. It was observed in our experimental that even though excessive arylaldehyde was introduced to the reaction system, there is a strong tendency for the formation of compounds **3**.
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