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One-Pot Tandem Double-Aldol Reaction/Aza-Addition of Acetylacetamides and *o*-Phthalaldehyde Leading to Spiroindan-2,2′-pyrrolidines

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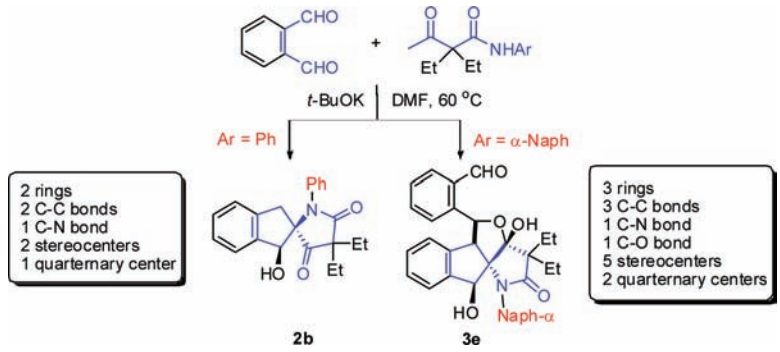
ABSTRACT



A novel domino reaction based on *o*-phthalaldehyde and 3-oxo-*N*-arylbutanamide 1 has been developed which allows one-pot and efficient synthesis of structurally complex spiroindan-2,2′-pyrrolidines 2 and 3 with complete regioselectivity and high stereoselectivity from acyclic precursors.

The domino reaction, an environmentally benign and atom-efficient process, plays an important role in organic synthesis.[1] In the last two decades, various types of domino reactions have been developed and employed in the synthesis of all kinds of cyclic compounds.[2] However, efficient construction of spiro compounds with stereochemical and structural complexities still remains a great challenge to synthetic chemists.[3] In our research on the syntheses of useful carbocyclic and heterocyclic compounds via domino reactions,[4] the synthetic potential of acetylacetamides has been demonstrated in the construction of furoquinolines,[5a] pyranoquinolines,[5b] martinellic acid derivatives,[5c] pyridin-2(1*H*)-ones,[5d−f] and 2,3-dihydrofurans.[5g] Recently, a new approach to pyrrolidine-2,4-diones was developed through a one-pot reaction of acetylacetamides and electron-deficient aryl (heteroaryl) aldehydes via a tandem aldol condensation/intramolecular aza-anti-Michael addition sequence.[6]

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(2) Selected examples on recent reports: (a) Elliott, G. I.; Fuchs, J. R.; Blagg, B. S. J.; Ishikawa, H.; Tao, H.; Yuan, Z.-Q.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10589–10595. (b) Appel, B.; Saleh, N. N. R.; Langer, P. *Chem.—Eur. J.* **2006**, *12*, 1221–1236. (c) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Shu, X.-Z.; Liang, Y.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7068–7071. (d) Pinto, A.; Neuville, L.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291–3295.

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In connection with these studies, we envisioned that the reaction between an aldehyde bearing a carbonyl group in the ortho-position and acetylacetamide would lead to the formation of structurally interesting spirolactams in a single step.[6,7] To this end, in our continuing research, the reactions of *o*-phthalaldehyde, with selected acetylacetamides **1** under basic conditions, were investigated.[8] As a result, a novel protocol for the synthesis of the spiroindan-2,2′-pyrrolidine derivatives **2** and **3**,was developed (For structures, see Figure 1). In a simple operation, two C−C bonds and one C−N bond were formed in the former and up to five new bonds (three C−C bonds, one C−N bond, and one C−O bond) and five stereocenters were created in the latter, depending on the steric effects of *N*-aryl substituent of acetylacetamides **1**. In this paper, the preliminary results on the synthesis of spirolactams **2** and **3** and a new strategy for the *construction of spiro compounds starting from acyclic precursors in a domino process* are described.

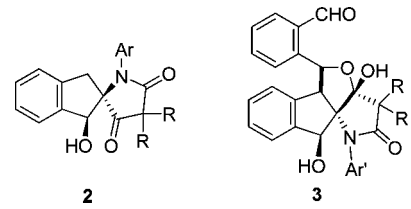
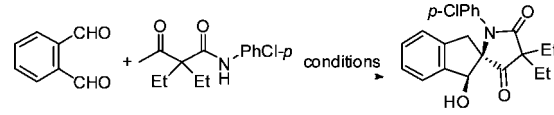


Figure 1. Structures of spiroindan-2,2′-pyrrolidines **2** and **3**.

In the initial study, optimization of the reaction conditions was conducted (Table 1). It was found that, at room temperature in NaOEt/EtOH or NaH/DMSO or at 60 °C in NaH/DMSO for 10 h, the reactions of *o*-phthalaldehyde and *N*-(4-chlorophenyl)-2,2-diethyl-3-oxobutanamide **1a** could not give satisfactory results (entries 1−3). To our delight, at 60 °C in KOBu^t (1.0 mmol)/THF (5.0 mL) for 1 h, the reactions of *o*-phthalaldehyde (1.0 mmol) and **1a** (1.0 mmol) gave a white solid after workup and purification by column chromatography, which was characterized as (4-chlorophenyl)-4′,4′-diethyl-1-hydroxy-1,3-dihydrospiro[indene-2,2′-pyrrolidine]-3′,5′-dione **2a** (27% yield, entry 5) on the basis of its spectral and analytical data (see the Supporting Information). The structure of **2a** and its stereochemistry was

Table 1. Optimization of the Spirocyclization Reaction of *o*-Phthalaldehyde with **1a**



1a **2a**

entry	base	solvent	T (°C)	time (h)	yield[b] (%)
1	NaOEt	EtOH	rt	10.0	no reaction
2	NaH	DMSO	rt	10.0	no reaction
3	NaH	DMSO	60	10.0	complicated
4	*t*-BuOK	DMF	rt	1.5	trace[c]
5	*t*-BuOK	THF	60	1.0	27
6	*t*-BuOK	DMF	60	0.4	50

[a] Reactions were carried out on a 1.0 mmol scale in 5.0 mL of solvent with *o*-phthalaldehyde (1.0 equiv), **1a** (1.0 equiv), and a base (1.0 equiv). [b] Yield of isolated product. [c] Only a trace amount of **2a** was detected with intact substrates.

(3) Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. For a review on the stereocontrolled synthesis of spiro compounds, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007–9071. For selected papers, see: (b) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1063–1066. (c) Chang, H.-K.; Datta, S.; Das, A.; Odedra, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744–4747. (d) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230–12231. (e) Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57–60. (f) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186–3189. (g) Huang, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 8060–8061. (h) Edmonson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138–1140. (i) Dai, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 3498–3499.

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(8) For a review on the reactions of *o*-phthalaldehyde with nucleophiles, see: (a) Zuman, P. *Chem. Rev.* **2004**, *104*, 3217–3238. For some recent papers on *o*-phthalaldehyde reactions, see: (b) Petrignet, J. T.; Roisnel, Grée, R. *Chem.—Eur. J.* **2007**, *13*, 7374–7384. (c) Ramana, C. V.; Reddy, C. N.; Gonnade, R. G. *Chem. Commun.* **2008**, *3151*, 3153. (d) Bornhoeft, J.; Siegwarth, J.; Nather, C.; Herges, R. E. *J. Org. Chem.* **2008**, *73*, 1619–1624. (e) Navarro, C.; Csákÿ, A. G. *Org. Lett.* **2008**, *10*, 217–219. For aldol reactions of *o*-phthalaldehyde with mono/dicarbonyl compounds, see: (f) Tarbell, D. S.; Wargotz, B. *J. Am. Chem. Soc.* **1954**, *76*, 5761–5767. (g) Dimroth, K.; Freyschlag, H. *Angew. Chem.* **1957**, *69*, 95–96. (h) Meuche, D.; Strauss, H.; Heilbronner, E. *Helv. Chim. Acta* **1958**, *41*, 2220–2229. (i) Davey, W.; Gottfried, H. *J. Org. Chem.* **1961**, *26*, 3699–3705. (j) Gazit, A. *J. Chem. Soc., Chem. Commun.* **1986**, *6*, 445–446. (k) Langer, P.; Albrecht, U. *Synlett* **2001**, *4*, 526–528. (l) Yadav, J. S.; Syamala, M. *Chem. Lett.* **2002**, *7*, 688–689. (m) Albrecht, U.; Nguyen, T. H. V.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3417–3424.

further confirmed by the X-ray single-crystal diffraction (Figure 2).[9] The yield of **2a** was improved to 50% when

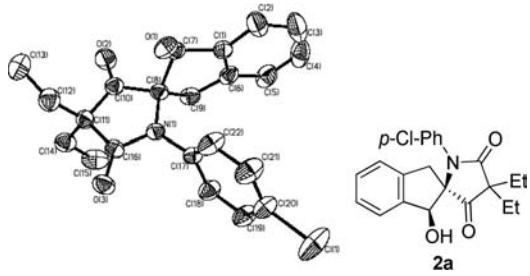
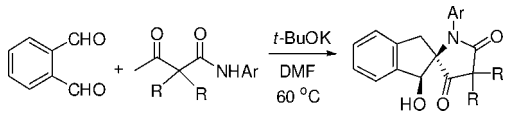


Figure 2. ORTEP drawing of **2a**.

DMF was used as the solvent, and the reaction was completed within 25 min at 60 °C (entry 6). In comparison, a trace of **2a** was produced when the reaction was performed at room temperature (entry 4) with a large amount of substrates remained intact. It was noteworthy that when the 4-ClPh substituent at the nitrogen of **1a** was displaced by an alkyl, for example, methyl, no reaction was observed by TLC monitoring under the optimized conditions as described in entry 6.

In the following work, the scope of the reaction based on *o*-phthalaldehyde and 3-oxo-*N*-arylbutanamides **1** was investigated. Under the optimized conditions (Table 2,

Table 2. Reactions of *o*-Phthalaldehyde with 3-Oxo-*N*-arylbutanamides Leading to Spiro Compounds **2**[a]



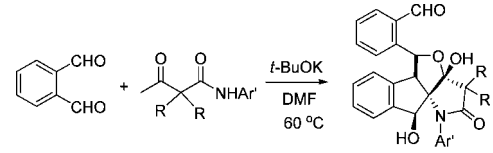
entry	1	Ar	R or (R,R)	time (min)	2[b]	yield[c] (%)
1	**1a**	4-ClPh	Et	25	**2a**	50
2	**1b**	Ph	Et	25	**2b**[d]	54
3	**1c**	4-MeOPh	Et	20	**2c**	57
4	**1d**	Ph	$(CH_2)_4$	25	**2d**	62
5	**1e**	4-ClPh	$(CH_2)_4$	20	**2e**	47
6	**1f**	4-MePh	$(CH_2)_4$	20	**2f**	53
7	**1g**	4-MeOPh	$(CH_2)_4$	25	**2g**	44
8	**1h**	2-ClPh	$(CH_2)_4$	25	**2h**	46
9	**1i**	2-MeOPh	$(CH_2)_4$	20	**2i**	53

[a] Reactions were carried out on a 1.0 mmol scale in 5.0 mL of DMF with *o*-phthalaldehyde (1.0 equiv), **1a** (1.0 equiv), and *t*-BuOK (1.0 equiv). [b] The stereochemistry of **2** was assigned by the single-crystal structure of **2a**. [c] Yield of isolated product. [d] Trace amounts of diastereomers of **2** were observed. Diastereomers of **2b** could be isolated in 7% yield as a side product.

entry 1), a range of reactions of *o*-phthalaldehyde (1.0 mmol) and selected 3-oxo-*N*-arylbutanamides **1** (1.0 mmol) were carried out at 60 °C in 5 mL of DMF (Table 2).[10] Consequently, in cases of **1b** (Ar = Ph) and **1c** (Ar = 4-MeOPh), the reactions were successful and resulted in good yields of desired spiro compounds **2b** and **2c**, respectively (Table 2, entries 2 and 3). On the other hand, 3-oxo-*N*-arylbutanamides **1** with a cyclopentane unit, for example **1d**−**i**,[5c,6] proceeded efficiently to afford the desired products **2d**−**i** in moderate to good yields (entries 4−9).[11] A literature search revealed that spiroindan-2,2′-pyrrolidine derivatives possess good analgesic activity.[12] However, their preparation requires multistep procedures. Clearly, a mild and efficient one-pot access to spiroindan-2,2′-pyrrolidines was developed herein.

In comparison with the results described in Table 2, entries 8 and 9 (Ar = 2-ClPh and 2-MeOPh), surprisingly, the reaction of *o*-phthalaldehyde (1.0 or 2.0 equiv) with acetylacetamide **1j** (Ar = 2-MePh) under identical conditions as above for 10 min gave **3a** exclusively (Table 3,

Table 3. Reactions of *o*-Phthalaldehyde with 3-Oxo-*N*-arylbutanamides Leading to Spiro Compounds **3**[a]



1 3

entry	1	Ar′	R or (R,R)	time (min)	3[b,c]	yield[d] (%)
1	**1j**	2-MePh	Et	10	**3a**	42
2	**1k**	2-MePh	$(CH_2)_4$	8	**3b**	64
3	**1l**	2,4-Me_2Ph	Et	10	**3c**	60
4	**1m**	2,4-Me_2Ph	$(CH_2)_4$	10	**3d**	45
5	**1n**	α-Naph	Et	10	**3e**	52
6	**1o**	α-Naph	$(CH_2)_4$	8	**3f**	65

[a] Reactions were carried out on a 1.0 mmol scale in 5.0 mL of DMF with *o*-phthalaldehyde (2.0 equiv), **1a** (1.0 mmol), and *t*-BuOK (1.0 equiv). [b] The stereochemistry of **3** was assigned by the single-crystal structure of **3b**. [c] No diastereomers were observed by NMR spectroscopy. [d] Yield of isolated product.

entry 1). The structure of **3a** was difficult to elucidate by ^{1}H and ^{13}C NMR spectra. Fortunately, the single-crystals of product **3b** could be obtained, which shows a core structure of spiroindan-2,2′-pyrrolidine with an additional fused furan ring (Figure 3).[9] Product **3b** was obtained in 64% yield from the reaction of *o*- phthalaldehyde (2.0 equiv) and **1k** under above conditions (Table 3, entry 2). The above reactions can be completed in even shorter time

(9) CCDC 694222 (**2a**) and CCDC 694223 (**3b**) contain the supplementary crystallographic data in the Cambridge Crystallographic Data Centre.

(10) For synthetic details, see the Supporting Information.

(11) Attempts (dry solvent and N_2 protaction/temperature, mole ratio variations, concentration) to further improve the yields of **2** and **3** were not encouraging at the present stage.

(12) For papers on spiro[indan-2,2′-pyrrolidines], see: (a) von Stoll, A. P.; Peteher, T. J.; Weber, H. P. *Helv. Chim. Acta* **1979**, *62*, 1223–1230. (b) Crooks, P. A.; Rosenberg, H. E. *J. Med. Chem.* **1978**, *21*, 585–587. (c) Sommerville, R.; Rosenberg, H. E.; Crooks, P. A. *J. Pharm. Sci.* **1985**, *74*, 553–555. (d) Crooks, P. A.; Rosenberg, H. E. *J. Chem. Soc., Perkin Trans. 1* **1979**, *2719*, 2726.

(approximately 10 min), and no intermediate could be isolated by changing the reaction conditions (ratio of reactants, temperatures, and reaction times). Interestingly, the stereochemistry of the spiroindan-2,2′-pyrrolidine core of **2** and **3** is different; i.e., the OH is *cis* to the *N*-aryl group in **2**, and *trans* in **3** (Figures 2 and 3). This may

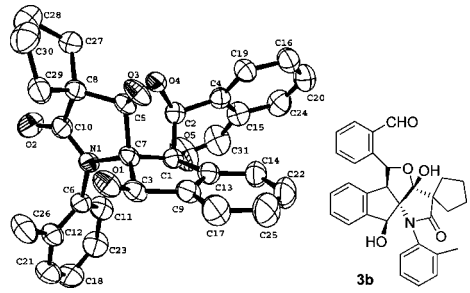
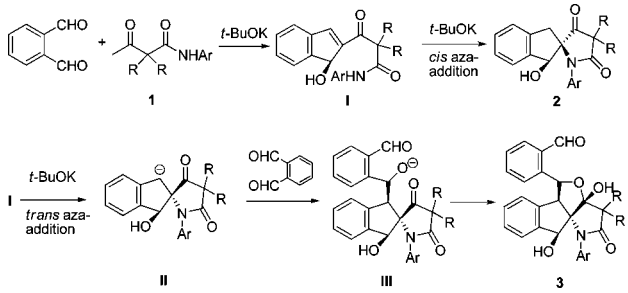


Figure 3. ORTEP drawing of **3b**.

mean that the reaction of *o*-phthalaldehyde and 3-oxo-*N*-arylbutanamide is highly diastereoselective and finely tuned by means of a selective choice of the *N*-aryl substituent of **1**. To further understand the contributions of the *N*-aryl of **1**, the reactions of **1l** and **1m** (Ar′ = 2,4-Me_2Ph), reactions of **1n** and **1o** (Ar′ = α-Naph), which have similar steric environments as **1j** and **1k**, with *o*-phthalaldehyde were then performed. Likewise, the corresponding desired products **3c**−**f** were obtained in good yields (Table 3, entries 3−6).[11]

In the reaction of *o*-phthalaldehyde with **1b** (Table 2, entry 2), the diastereomers of **2b** were isolated in 7% yield as a minor side product. Comparatively, no diastereomers could be found for the reactions of *o*-phthalaldehyde with **1j**−**o** (Table 3), and in all cases, no corresponding regioisomers were detected for reactions of *o*-phthalaldehyde with **1a**−**o** (Tables 2 and 3). On the basis of all the results described, a possible mechanism for the highly efficient one-pot transformation into spirocycles **2** and **3** was proposed, as shown in Scheme 1.

Scheme 1. Proposed Mechanism for the Formation of Spirocycles **2** and **3**



Initially, sequential intermolecular and intramolecular aldol reactions are supposed to occur by attack of active methyl onto the two formyl groups of *o*-phthalaldehyde, respectively, releasing a molecular of water to generate the key intermediate **I**.[8] Then an intramolecular aza-conjugate addition (5-exotrig cyclization)[6,13] of **I** in a regiospecific manner takes place to give the azaspirocyclization product **2** or intermediate **II**.[14] Regarding the stereochemistry, there are two alternative ways depending on the steric effects of the *N*-aryl group of 3-oxo-*N*-arylbutanamide **1**. On one hand, the intramolecular aza-addition *cis* to the hydroxyl group of **I** (intramolecular hydrogen bond between hydroxy and amide is favorable for this type of addition) gives rise to spiroindan-2,2′-pyrrolidines **2** (Table 2). On the other hand, when the *N*-aryl substituent of **1** is 2-methylphenyl, 2,4-dimethylphenyl- or α-naphthyl (Table 3), the *cis*-aza-addition is restricted, most probably due to the peri-effect.[15] Thus, the aza-addition *trans* to the hydroxyl group would occur and initiate further reactions, i.e., an intermolecular aldol reaction followed by intramolecular hemiacetalization (**II** → **III** → 3) to give fused spiroindan-2,2′-pyrrolidines **3** (Table 3). Clearly, the proposed mechanism is consistent with the stereochemistry. In the reactions explored here, three covalent bonds are sequentially formed (two C−C bonds and one C−N bond) at the active methyl group of acetylacetamides **1**, which represents an unusual example of *conversion of a primary carbon atom to a spiro quarternary carbon atom* in one step.[16]

In conclusion, we have described a novel methodology which provides direct access to spiroindan-2,2′-pyrrolidines with complete regioselectivity and very high stereoselectivity. The reaction process employs readily available *o*-phthalaldehyde and 3-oxo-*N*-arylbutanamide as acyclic precursors and involves tandem aldol/aldol condensation (to form the indan ring) and intramolecular aza-conjugate addition (to form the spiro linkage) sequences. The reaction features cheap reagents, mild conditions, high efficiency, and metal catalyst-free conditions. Further exploration of the domino strategy and their applications in the synthesis of other types of spirocycles are in progress.

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Supporting Information Available: Experimental details and characterization for all new compounds and crystal structure data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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