ORGANIC
LETTERS

2007
Vol. 9, No. 14
2669−2672

Highly Selective Cascade Couplings for the Syntheses of Functionalized Piperidinones and Bispidines

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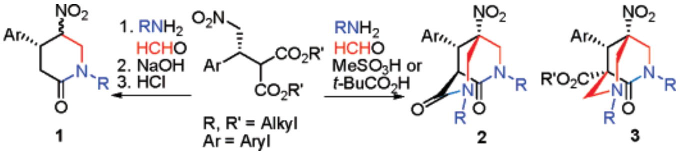
Received April 18, 2007

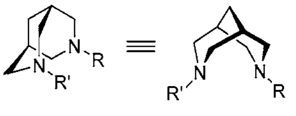
ABSTRACT



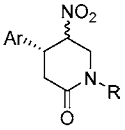
Efficient cascade couplings to synthesize functionalized piperidinones 1 and bispidines 2 and 3 have been developed. Simple modifications to the reaction conditions allow for the highly controlled and selective formation of each compound. In addition, the *cis* isomer of 1 can be selectively obtained under acidic conditions, while the preparation of the corresponding *trans* isomer can also be readily realized through a base-catalyzed, dynamic crystallization-driven process.

The core structures of bispidine[1] (3,7-diazabicyclo[3.3.1]nonane) and piperidine exist in large numbers of natural and unnatural pharmaceutically and biologically important compounds. In addition, the unique, rigid backbone of bispidine provides an attractive platform to develop new ligands for various transformations[2] because the defined cavity between the nitrogen atoms is well positioned for chelation to a Lewis acid center such as a metal ion.

Recently, we required a practical and efficient synthesis of piperidinones **1**, which are key intermediates for the preparation of a variety of pharmaceutically important drug candidates.[3] Although various methods have been developed for the preparation of lactams and cyclic amines, efficient asymmetric preparation of bispidines[4,5] as well as functionalized piperidinones **1**[6] has been limited.



Bispidine



1

Application of multiple component couplings to synthesize organic molecules efficiently and practically is a desired strategy,[7] as multiple transformations can be achieved through a series of cascade reactions. We envisioned that access to **1** could arise from **5** through coupling three

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[1] Bispidine skeleton is the backbone of the family of lupinine-cytisine-sparteine-matrine alkaloids.

[2] For recent examples, see: (a) Born, K.; Comba, P.; Ferrari, R.; Lawrance, G. A.; Wadepohl, H. *Inorg. Chem.* **2007**, *46*, 458. (b) Bukowski, M. R.; Comba, P.; Lienke, A.; Limberg, C.; Lopez de Laorden, C.; Mas-Ballesté, R.; Merz, M.; Que, L., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 3446. (c) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378. (d) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480 and references therein.

[3] For recent examples, see: (a) Cox, J. M.; Edmondson, S. D.; Harper, B.; Weber, A. E. PCT Int. Appl. WO2006039325, 2006. (b) Edmondson, S. D.; Mastracchio, A.; Cox, J. M. PCT Int. Appl. WO2006058064, 2006. (c) Ashwell, S.; Gero, T.; Ioannidis, S.; Janetka, J.; Lyne, P.; Su, M.; Toader, D.; Yu, D.; Yu, Y. PCT Int. Appl. WO2005066163, 2005. (d) Cody, W. L.; Holsworth, D. D.; Powell, N. A.; Jalaie, M.; Zhang, E.; Wang, W.; Samas, B.; Bryant, J.; Ostroski, R.; Ryan, M. J.; Edmunds, J. J. *Bio. Med. Chem.* **2004**, *13*, 59.

[4] For recent examples, see: (a) Stead, D.; O'Brien, P. *Tetrahedron* **2007**, *63*, 1885. (b) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (c) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577 and references therein.

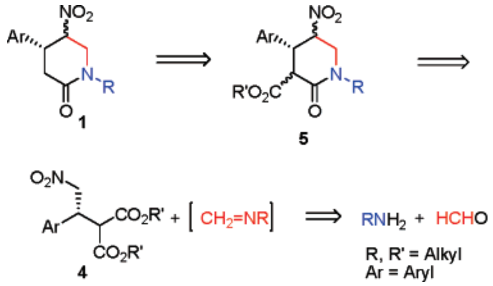
[5] For a recent review, see: Lesma, G.; Sacchetti, A.; Silvani, A.; Danieli, B. *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; Research Signpost, 2005, 33.

[6] For examples, see: Kumar, S.; Flamant-Robin, C.; Wan, Q.; Chiaroni, A.; Sasaki, N. A. *J. Org. Chem* **2005**, *70*, 5946 and references therein.

10.1021/ol070909n CCC: $37.00

components: a nitroalkane **4**, a primary amine, and formaldehyde (Scheme 1). Enantiomerically pure **4** can be obtained in one step by taking advantage of recent methodology for the enantioselective Michael addition of malonates to nitrostyrenes.[8] Elaboration of the resulting nitroalkanes has not been well studied, and to our knowledge,[9,10] this type of three-component coupling has not been reported. In this communication, we report a cascade three-component coupling that not only results in a one-pot preparation of functionalized piperidinones **1** as designed but also enables one-step construction of bispidines **2** or **3**, either of which can be selectively synthesized by simply modifying the reaction conditions.

Scheme 1. Retrosynthetic Analysis

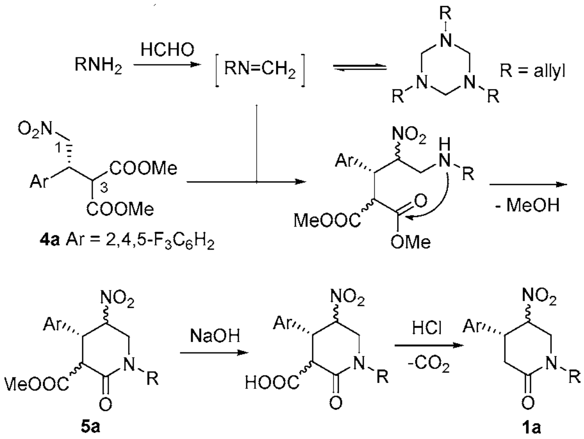


2

3

Our studies initially focused on a practical synthesis of substrate **1a**. Allyl amine became our amine of choice[11] due to the ease of selective deprotection of the allyl group, which offers the potential for further functionalization of the coupling products **5**. After several experiments, we were pleased to find that the desired product **5a** (Ar = 2,4,5-trifluorophenyl, R = allyl) could be obtained as a mixture of isomers in 90% yield by treatment of the corresponding **4a** with 1.3 equiv of allyl amine and 1.05 equiv of aqueous HCHO in *i*-PrOH at 50 °C (Scheme 2). The steric hindrance and pK_a differences between the C-1 H adjacent to the nitro group and the C-3 H adjacent to the two ester groups were believed to suppress the formation of potential competition products through Mannich reaction on C-3, which were not observed under our reaction conditions. Without workup, the crude reaction mixture was treated with NaOH followed by decarboxylation upon acidification to give a mixture of *cis/trans* **1a** (Ar = 2,4,5-trifluorophenyl, R = allyl).

Scheme 2. Three-Component Coupling and Its Plausible Pathway to Piperidinones[11,12]



It is interesting to note that the *cis* isomer of **1a** is the major product upon decarboxylation. However, early results showed that the decarboxylation conditions, such as reaction time, pH, and temperature, could affect the *cis/trans* ratio significantly.

In order to gain control of the *cis/trans* stereochemistry of the coupling products **1**, we further screened various conditions to prompt the epimerization of the nitro group of piperidinones **1**. Under acidic epimerization conditions (Table 1), the *cis*-piperidinones are the dominant product in a homogeneous reaction solution.[13] The *cis/trans* ratio of **1a**

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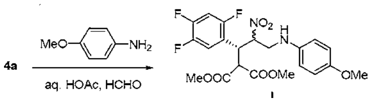
(7) For recent reviews, see: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(8) For examples, see: (a) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (b) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958. (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 12172. (d) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *127*, 9906. (e) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148. (f) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215.

(9) For similar three-component couplings, see: (a) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Org. Chem.* **2003**, *68*, 2467. (b) Desai, M. C.; Lefkowitz, S. L. *BioMed. Chem. Lett.* **1993**, *3*, 2083. (c) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831. (d) Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, 615.

(10) For recent examples of multiple component coupling involving nitroalkane or amine/formaldehyde, see: (a) Enders, D.; Hüttlm, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Sunden, H.; Ibrahem, I.; Eriksson, L.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2 and references therein. (c) During the preparation of this paper, synthesis of derivatives **2** was reported: Pei, Z.; Li, X.; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983.

(11) The use of other alkyl amines, such as 4-methoxybenzyl amine and 3,4-dimethoxybenzyl amine, also gave the desired coupling products. However, aryl amines such as 4-methoxyphenyl amine led to the formation of **I**, presumably due to the less nucleophilic aryl amine nitrogen. The formation of **I** thus further supports the stepwise reaction pathway (Scheme 2).

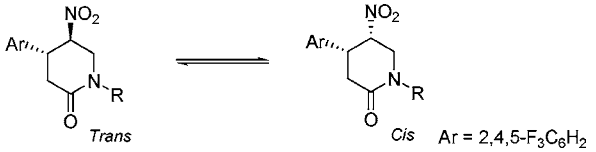


I

(12) RN═CH2 imine is an unstable intermediate; see: Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 1635.

(13) It is not very clear why the *cis* isomer is the major product through acidic equilibrium. Presumably, the formation of the *cis* isomer is kinetically favored under acidic conditions. The isolated *cis*-**1a** is partially converted to the *trans* isomer after several weeks at ambient temperature.

Table 1. Epimerization of Piperidinones **1**[a]



entry	R	conditions	*trans/cis*[14]
1	*p*-MeO−$C_6H_4CH_2$	HCl, aq MeOH, 55 °C	1:15
		DBU, THF, rt	5:1
2	H	HCl, *n*-PrOH, 55 °C	1:25
3	$CH_2{=}CHCH_2$	HCl, aq *i*-PrOH, 55 °C	1:32
		$NaHCO_3$, aq *i*-PrOH, 45 °C	2:1

[a] All reactions were homogeneous.

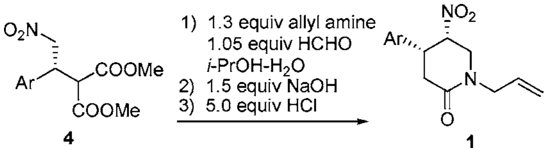
could be as high as 97:3. In contrast, epimerization of the *cis* isomer of **1a** to its corresponding thermodynamically favored *trans* isomer could be realized upon exposure to weak bases; however, poor *cis/trans* ratios in favor of the *trans* isomer were obtained.

Interestingly, the selective formation of the *trans* isomer of **1** was achieved by designing a base-catalyzed, dynamic crystallization-driven process to allow the *cis* isomer in the supernatant to continuously equilibrate to the favored *trans* isomer under basic conditions, while the thermodynamically favored *trans* isomer gradually crystallizes from the reaction solution. In practice, the crude reaction mixture after decarboxylation was pH-adjusted to pH = 7−8 by aqueous $NaHCO_3$. Upon aging at 45 °C, the desired *trans* isomer of **1a** was crystallized and directly isolated from crude aqueous *i*-PrOH solution though a simple filtration in 76% overall isolated yield and >98 area % purity (HPLC). Only about 1−2% of the undesired *cis* isomer of **1a** remained in the mother liquor.[15,16] Thus, selective preparation of both *cis*- and *trans*-piperidinones **1** can be realized in a controlled manner.

We next investigated the one-pot three-component coupling for a set of aryl nitro diesters **4**. As shown in Table 2, the three-component coupling reaction works extremely well with various nitro malonate substrates **4**. After acidic decarboxylation/equilibration, for all substrates we examined, the *cis*-piperidinones were formed in high diastereoselectivity, in one pot.

During our study on optimizing the cascade coupling to prepare piperidinone **1a**, two byproducts which formed in few percent under certain conditions[17] were isolated and characterized as **2a** and **3a** (Ar = 2,4,5-trifluorophenyl, R = allyl). The plausible pathways to form **2a** and **3a** are outlined in Scheme 3. The identification of **2a** and **3a** encouraged us to further investigate the cascade coupling in order to selectively synthesize **2** or **3** by promoting the

Table 2. One-Pot Synthesis of Piperidinones **1**

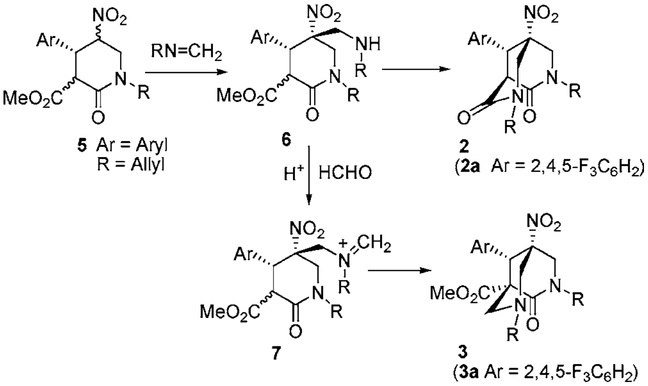


entry	Ar	*cis* / *trans*[14]	yield (%)[a]
1	4-FC_6H_4	15:1	81
2	C_6H_5	25:1	74
3	4-ClC_6H_4	10:1	72
4	4-MeC_6H_4	9:1	81
5	3-pyridine	18:1	65
6	4-$MeOC_6H_4$	17:1	62

[a] Isolated yield of the *cis*-**1** over three steps. For experimental procedures, see Supporting Information.

subsequent Mannich−amidation or Mannich−Mannich cascades. The non-epimerizable aryl group in **5** is also believed to play a key role to set up the stereochemistry of the two new stereogenic centers in **2** and **3** created via the second cascade coupling. The $RN{=}CH_2$ approaches **5** from the less hindered side, opposite the Ar group, which leads to intermediate **6** to establish a *cis* relationship of NO_2 and Ar.

Scheme 3. Plausible Pathways to Bispidine Derivatives **2** and **3**



In order to stimulate the second three-component cascade coupling, we need to establish reaction conditions that also allow epimerization of the NO_2-bearing center as well as the ester group in **5**, so all isomers of **5** can be utilized. On the basis of our observation that *trans*-piperidinone **1** favored isomerization to its *cis* isomer under acidic conditions, we thus started to explore the acid effects on the three-component coupling reaction. We also reasoned that introducing an appropriate acid to the reaction would facilitate the process to generate the possible iminium intermediate **7**, which affords **3** subsequently.

As shown in Table 3, in the absence of acids and presence of 3.2 equiv of formaldehyde, the second cascade coupling reaction can proceed but with low selectivity (**2** vs **3**) (Table 3, entry 1). The formation and consumption of the isomers

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(14) Unless otherwise mentioned, the ratio of *cis/trans* or diastereoisomers was determined by HPLC analysis (YMC Pack Pro C18, 5 μm particle size, 250 × 4.6 mm, mobile phase: 10 mM H_3PO_4/MeCN).

(15) Successfully demonstrated in 6 kg scale.

(16) For example, the *trans*-piperidinone (R = H, Table 1) can also be isolated in the same way.

(17) In particular, when formaldehyde was overcharged.

Table 3. Selected Results for Selective Preparation of **2a** and **3a** from **4a**[a]

entry	acid		**2a**:**3a**
1	none	none	1:1.4[b]
2	HOAc	0.2 equiv	1.5:1[b]
		2.5 equiv	3.2:1[b]
		10 equiv	1.1:1[b]
3	$MeSO_3H$	3.0 equiv	no reaction
		0.5 equiv	1:14; 80% yield
4	CF_3CO_2H	0.5 equiv	1:12
5	t-$BuCO_2H$	0.5 equiv	16:1; 86% yield

[a] In a typical experiment, to a solution of **4a** (ca. 0.2 M) and allyl amine (2.5 equiv) in *i*-PrOH/H_2O (ca. 5:1) in the presence or absence of an acid (as specified in Table 3) was added aqueous HCHO (12 wt %, 3.2−6 equiv) dropwise at 50−60 °C over 1.5−3 h. The reaction was agitated at 50−60 °C for several hours until the reaction was completed. [b] The reaction was run at about 0.5 M of **4a**.

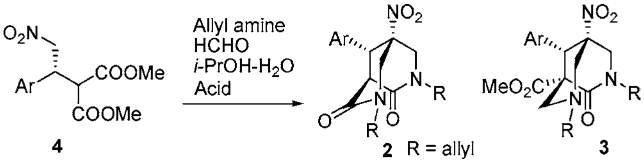
of **5** can be clearly monitored by HPLC as the cascade coupling reaction proceeds. The use of HOAc does not improve the selectivity, but interestingly, the ratio of **2**:**3** is reversed in comparison to the use of strong acid or no acid (Table 3, entries 1, 3, and 4). The amount of HOAc charged in the reaction also affected the ratio of **2**:**3**. However, introducing excess strong acid, such as $MeSO_3H$, unlike the use of excess weak acid HOAc, does shut down the reaction as 2.5 equiv of allyl amine is expected to be fully protonated. However, *the use of a catalytic amount of a strong acid, such as CF_3CO_2H or $MeSO_3H$, dramatically affected the reaction pathways such that the bispidine **3a** became the dominant product.* Although 0.5 equiv of CF_3CO_2H or $MeSO_3H$ was mixed with 2.5 equiv of allyl amine, the H^+ liberated through equilibrium between the protonated amine salts[18] and amines is apparently good enough to promote the formation of the possible iminium intermediate **7**, which in turn affords **3** through cascade intramolecular Mannich reaction.

Encouraged by these results, we further examined the effect of weak acids. By adding a weak acid to the reaction solution in the presence of amines, the reactivity of amine species would not be attenuated much.[19] The amine group in intermediate **6** is, therefore, more readily available to be intramolecularly captured by the ester group to form **2** in the presence of weak acids than in the presence of strong acids. Dramatically, as 0.5 equiv of t-$BuCO_2H$ ($pK_a = 5.0$) was added to the reaction solution, a sharp turnover in selectivity was obtained. In contrast to the use of strong acids, which favor the formation of **3a**, a reversal in selectivity (**2a**:**3a** = 16:1) was obtained.

Thus, *either bispidines **2a** or **3a** can be selectively prepared by using an appropriate acid to influence the reaction pathways of the cascade three-component couplings,* which allows for excellent control of the three stereogenic centers of **2a** or **3a**.

Building on these results, we next explored the scope of the cascade reaction with various substrates. As shown in Table 4, in the presence of t-$BuCO_2H$, bispidine derivatives **2** were obtained in high selectivity for all substrates. The cascade multiple coupling is very effective and gives **2** in high yield. In contrast, the use of a strong acid results in a remarkable reversal in the selectivity, which leads to the formation of **3** selectively.

Table 4. One-Step Syntheses of **2** and **3**



entry	Ar	acid	**2**:**3**	yield (%)[a]
1	4-ClC_6H_4	t-$BuCO_2H$	21:1	88
		$MeSO_3H$	1:11	75
2	4-MeC_6H_4	t-$BuCO_2H$	34:1	91
		$MeSO_3H$	1:11[b]	70
3	C_6H_5	t-$BuCO_2H$	30:1	92
		$MeSO_3H$	1:7.2	78
4	2,4-$(MeO)_2C_6H_3$	t-$BuCO_2H$	22:1	92
		$MeSO_3H$	1:8	72
5	4-$MeOC_6H_4$	t-$BuCO_2H$	35:1	89
		$MeSO_3H$	1:12	72
6	4-FC_6H_4	t-$BuCO_2H$	23:1	85
		$MeSO_3H$	1:11	78
7	3-pyridine	t-$BuCO_2H$	25:1	88
		$MeSO_3H$	1:12[c]	74

[a] Isolated yield of the major product. For reaction conditions, see Table 3. [b] $MeSO_3H$ (1.0 equiv) and allyl amine (6.0 equiv) were used. [c] $MeSO_3H$ (1.5 equiv) and allyl amine (4.0 equiv) were used.

In summary, we have developed an efficient cascade coupling reaction, which leads to the selective preparation of piperidinones **1** or bispidine derivatives **2** or **3**. The selectivity of the reaction can be dramatically influenced by very simple modification of the reaction conditions. In the presence of 1 equiv of formaldehyde and in the absence of acid, **5** can be selectively prepared in high yield. The *cis*-piperidinone **1** is obtained in high selectivity under acidic decarboxylation conditions, while the corresponding *trans* product **1** can also be prepared in high yield and purity through a base-catalyzed, dynamic crystallization-driven process. However, in the presence of t-$BuCO_2H$ or strong acid, such as $MeSO_3H$, selective one-step synthesis of bispidine derivatives **2** or **3** can also be easily achieved.

Supporting Information Available: Experimental details for the preparation of **1**, **2**, and **3**, as well as their characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) It is reported that the counteranion of protonated amines can also affect the rate of Mannich reaction; see: Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2005**, *70*, 4248.

(19) Xu, F.; Armstrong, J. D.; Zhou, G. X.; Simmons, B.; Hughes, D.; Ge, Z.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **2004**, *126*, 13002.