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A Novel Diastereoselective Multicomponent Cascade Reaction

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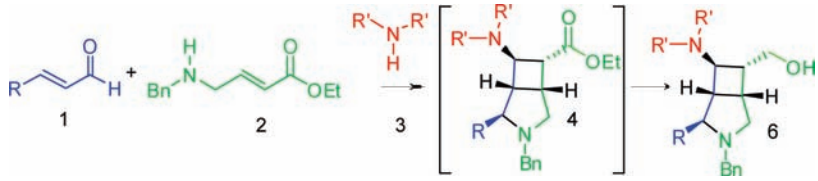
ABSTRACT

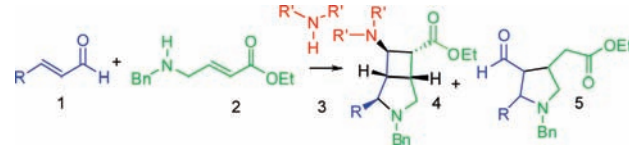


A novel multicomponent cascade reaction led to the formation of a strained 3-azabicyclo[3.2.0]heptane derivative 4. The unstable ester 4 was reduced in a one-pot procedure to a stable alcohol 6. The formation of the bicyclic product is highly diastereoselective, predominantly affording one diastereoisomer. The obtained azabicycloheptanes are important pharmacophores.

Synthetic organic chemistry has reached a turning point in which a new paradigm is needed.[1] A traditional single-step procedure affording only one (or two) new chemical bond(s) will be replaced by more efficient multicomponent cascade or domino reactions. The number of protective groups decreases and atom-efficiency and step-efficiency increase by using these approaches. The chemistry of multicomponent and domino reactions which started with the pioneering work of Ivar Ugi[2] is now developing quickly and well-documented in the literature.[3,4]

In the course of our ongoing investigations in the field of aminocatalysis,[5] we discovered a new and unexpected multicomponent cascade reaction (Scheme 1). The reaction of α,β-unsaturated aldehyde **1**, *N*-benzylaminocrotonate **2**, and secondary amine **3** afforded the expected pyrrolidine derivative with general formula **5** as well as the bicyclic product with general formula **4**. The formation of the monocyclic product can be rationalized by the organocatalytic domino aza-Michael reaction via iminium−enamine

Scheme 1. Reaction between α,β-Unsaturated Aldehyde **1**, *N*-Benzylaminocrotonate **2**, and Secondary Amine **3**



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activation as described recently by Wang et al.[6] However, we found that if we use two secondary amines (instead of sulfonamide and amine like Wang), the sterically less demanding amine **3** can be incorporated into the target through 3,4-*cis* substitution of the pyrrolidine intermediate, leading to the formation of the highly strained tetrasubstituted 3-azabicyclo[3.2.0]heptane derivative **4**.

This new chemical reaction leads to structures which are known to act as pharmacophores in modulating the dopamine D_3 receptor[7] (treatment of schizophrenia, depression, and Parkinson's disease (belaperidone),[8] in antibacterial agents (ecenofloxacin),[9] and in antitumor drugs (mitindomide).[10] The strained azabicyclo[3.2.0]heptane skeleton is an interesting tool for synthetic chemists engaged in the synthesis of natural products.[11]

However, in our first experiments, we achieved low selectivity between the formation of bicycle **4** and pyrrolidine derivative **5**. Therefore, we further investigated the reaction in more detail in order to get azabicyclo[3.2.0]heptane skeleton more selectively.

The reaction of cinnamaldehyde (**1**: R = Ph), *N*-benzylaminocrotonate **2**, and diethyl amine (**3**: R′ = Et) was selected as a model reaction, and various solvents were screened under different reaction conditions (Table 1).

Table 1. Reaction of Cinnamaldehyde (**1**: R = Ph), *N*-Benzylaminocrotonate **2**, and Diethylamine (**3**: R′ = Et)[a]

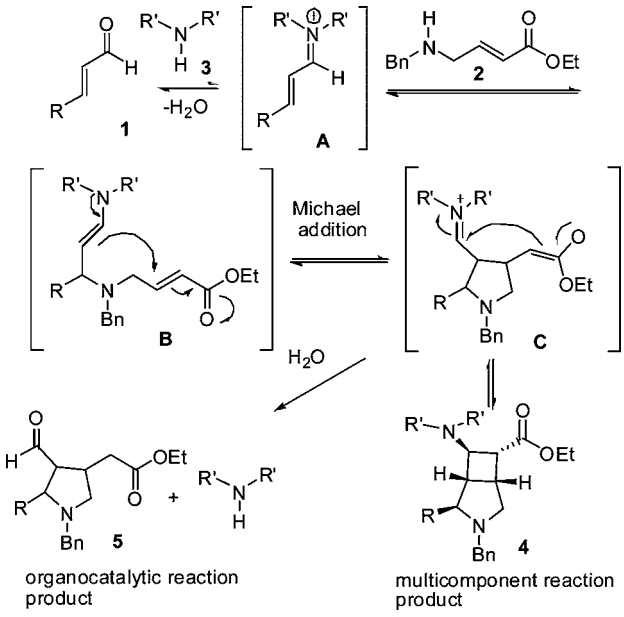
entry	solvent	ratio of **4**:**5**	yield of **4** (%)	yield of **5** (%)
1	CH_2Cl_2	3:1	60	19
2[b]	CH_2Cl_2	3.8:1	53	14
3[c]	CH_2Cl_2	6.3:1	70	11
4	toluene	1:2	22	40
5	CH_3CN	1:1.4	27	38
6	CCl_4	1:1.6	30	48
7[d]	$CHCl_3$	2:1	59	30

[a] Cinnamaldehyde (1 equiv), Et_2NH (1.1 equiv), and *N*-benzylaminocrotonate (1 equiv) were stirred in an appropriate solvent at rt for 24 h. [b] Molecular sieves (4 Å) were added. [c] Cinnamaldehyde (2 equiv), Et_2NH (2 equiv), and *N*-benzylaminocrotonate (1 equiv) were stirred in the presence of molecular sieves. [d] MW irradiation: 10 W, 30 min, 50 °C (internal cooling).

When the reaction was carried using approximately equimolar amounts of reagents in CH_2Cl_2, the ratio of obtained products was 3:1 (Table 1, entry 1). Elimination of water from the reaction media using molecular sieves favored the formation of the bicyclic compound **4** (Table 1, entry 2). Increasing concentration of the cinnamaldehyde and the secondary amine 2× to force the formation of the iminium intermediate led to substantial improvement in the selectivity, and bicyclic compound **4** was obtained in 70% of the isolated yield (Table 1, entry 3). Toluene, acetonitrile, $CHCl_3$, and CCl_4 considerably increased the amount of the pyrrolidine derivative **5** (Table 1, entries 4−7).

Formation of the bicyclic compound **4** is highly diastereoselective. In the best case, the diastereoisomeric ratio of main 2-*exo*-Ph isomer of compound **4** (as depicted in Scheme 1), and its minor 2-*endo*-Ph isomer was 25:1 (determined from the crude product by ^{1}H NMR). To our surprise, the diasteromeric ratio of the isolated products (17:1) and the ratio of isolated compounds **4** and **5** were much smaller than in the crude mixture. This data revealed that two competitive and reversible reactions take place simultaneously: the organocatalytic reaction affording pyrrolidine product and the multicomponent reaction leading to the bicyclic product. The proposed pathways of the competing reactions are outlined in Scheme 2. The presented mechanism can be

Scheme 2. Proposed Pathway of the Reaction



rationalized as follows: formation of iminium ion **A** activates unsaturated aldehyde **1**, and that leads to aza-Michael addition of amine **2** to **A**, affording intermediate **B**.[12] As in every iminium-activated aza-Michael reaction, discrimination between two secondary amines takes place.[13] Alkyl amine **3** participates in the formation the iminium ion, whereas amino crotonate **2** acts as a nucleophile. Intermediate **B** undergoes a second, intramolecular Michael reaction where enamine acts as a nucleophile and the crotonate subunit as an electrophile, leading to the intermediate **C**. This is a crucial intermediate of the transformation: it may hydrolyze

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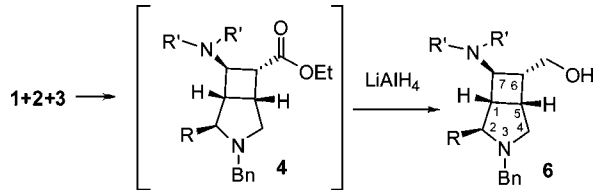
to a pyrrolidine derivative **5** or undergo an intramolecular Mannich-type ester enolate attack to iminium ion, affording a highly strained tetrasubstituted bicyclic compound **4**.[14] Reversibility of the reactions causes decrease in the ratio of compounds **4** and **5** (apparent as a change in the product ratio) during workup and purification.

Reduction of the ester group excludes the possibility of the retro-reactions. When we reduced the unstable esters **4** in one-pot procedure to the corresponding alcohols **6** with $LiAlH_4$, no later isomerization was detected during workup and other manipulations (Scheme 3).[15]

Scheme 3. Synthesis of Alcohols **6** via a One-Pot Procedure



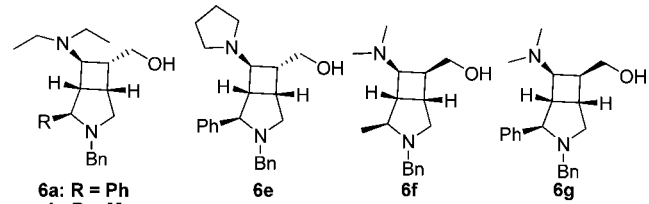
Anhydrous conditions (molecular sieves and anhydrous CH_2Cl_2) favor the multicomponent reaction, and the competing formation of the pyrrolidine derivative **5** is suppressed. Indeed, when the reaction was run under strictly anhydrous conditions, the pyrrolidine derivative **5** was formed only as a minor byproduct (<5%) and because of that it was not further isolated in the following experiments (see the Supporting Information for the experimental details).

Having improved the reaction conditions to achieve practically useful levels, the scope of the reaction was investigated. As presented in Table 2, various α,*β*-unsaturated aldehydes **1** and secondary amines **3** react with *N*-benzylaminocrotonate **2** to afford after reduction substituted bicyclic compound **6**.

The reaction was run in CH_2Cl_2 at room temperature using a 2-fold excess of aldehyde **1** and amine **3,** followed by a change of the solvent and reduction with $LiAlH_4$. The isolated yield of the single diastereoisomer of bicyclic compound **6** was generally high. The highest yield was obtained with dimethylamine and crotonaldehyde (entry 6). The cyclic secondary amine (pyrrolidine) reacted with lower yield (52%, entry 6) than acyclic amines.

The discovered multicomponent reaction is highly diastereoselective, affording predominantly one diastereoisomer **6** in a 2-*exo*,6-*endo*,7-*exo* configuration. The main factor that governs the stereodifferentiation is a steric hindrance of the substituent in α,*β*-unsaturated aldehyde **1**. Sterically more demanding derivatives of cinnamaldehyde gave the most diastereoselective reactions (the ratio of 2-*exo* and 2-*endo* isomers up to 45:1, entry 1). Diastereoselectivity was even higher in the case of *o*-nitrocinnamaldehyde. Because of the intolerance of the nitro group to the reduction with $LiAlH_4$ the diastereomeric ratio in that case was determined in the crude product of ester **4h** (entry 8). The only exceptions from the described general tendency are compounds **6f** and **6g**, whose main diastereoisomers have an *all-cis* configuration (entries 6 and 7).

Table 2. Synthesis of Azabicycles **6a**−**h**



6a: R = Ph
b: R = Me
c: R = Et
d: R = p-MeO-Ph

entry	compound **1**, R	amine **3**	time (h)	product	yield[a] (%)	dr[b]
1	Ph	Et_2NH	17	**6a**	68	45:1
2	Me	Et_2NH	24	**6b**	64	8:1
3	Et	Et_2NH	24	**6c**	65	8:1
4	*p*-MeOPh	Et_2NH	42	**6d**	66	24:1
5	Ph	pyrrolidine	24	**6e**	52	7:1
6	Me	Me_2NH (2 M in THF)	24	**6f**	73	6.5:1[c]
7	Ph (2 M in THF)	Me_2NH	24	**6g**	69	5:1[c]
8	*o*-NO_2Ph	Et_2NH	29	**4h**	ND	65:1[d]

[a] Isolated yield of the major diastereoisomer. [b] Diastereomeric ratio determined from the crude mixture by NMR. [c] Ratio of 6-*exo*/6-*endo* diastereoisomers. [d] Determined in the crude product of ester.

We also investigated the possibilities of the asymmetric version of the discovered multicomponent reaction. We assumed that the absolute stereochemistry of the product is determined by aza-Michael addition. Therefore, first we tried the auxiliary-based methods in which the multicomponent reaction was performed with enantiomerically pure aminocrotonate derivatives derived from (*S*)-α-methylbenzylamine or (*S*)-phenylalanine methyl ester and 4-bromocrotonate. However, in that case, a racemic product was obtained. Next, several organocatalysts (quinidine, cinchonine, (*R*)-TRIP) were used in different experiments under typical conditions.[16] Unfortunately, none of the catalysts showed any stereochemical induction.

The structures and relative configurations of 2,3,6,7-tetrasubstituted 3-azabicyclo[3.2.0]heptane derivatives were determined by a detailed $^1H-^{13}C$ NMR analysis, using 2D FT COSY, HSQC, and HMBC methods, including chemical shift and coupling constant analysis. The useful benchmark compounds for the chemical shift analysis are the unsubstituted bicyclo[3.2.0]heptane and *N*-3-benzyl-3-azabicyclo-

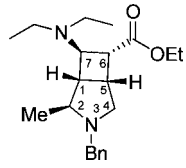
(14) Photochemical cycloaddition leading to disubstituted 3-azabicyclo[3.2.0]-heptane: (a) Bach, T.; Krüger, C.; Harms, K. *Synthesis* **2000**, 305–320. (b) Bach, T.; Pelkmann, C.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 2103–2104.

(15) General method for the multicomponent synthesis of substituted 3-azabicyclo[3.2.0]heptanes: To a solution of the corresponding aldehyde **1** (0.4 mmol) in CH_2Cl_2 (1.0 mL) were added dialkylamine **3** (0.4 mmol), *N*-benzylaminocrotonate **2** (0.2 mmol), and 4A molecular sieves. The mixture was stirred at room temperature for 24 h. Molecular sieves were filtered, and solvent was evaporated under reduced pressure. The crude bicyclic ester was dissolved in THF and reduced with $LiAlH_4$.

(16) Recent review of organocatalytic aza-Michael reaction: Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058–11076.

[3.2.0]heptane (although, only partially assigned).[17] These data show that the introduction of the benzyl-substituted nitrogen has a very small NMR effect on the four-membered ring. ^{13}C chemical shifts and $^{1}H-^{1}H$ spin−spin coupling constants from a four-membered ring determine the configuration of substituents on 3-azabicyclo[3.2.0]heptane skeleton. The representative data for 2-*exo* and 2-*endo* isomers of **4b** (the substitution pattern is the same as in compound **6b**) are given in Table 3. Relative configuration at C-2 is determined by three-bond coupling constants between the H-1 and H-2: for the 2-*endo* proton this coupling is 1.2 Hz (generally in present samples from 0 to 1.9 Hz) and for the 2-*exo* proton 5.4 Hz (in the **6a** *endo*-Ph isomer it is 6.7 Hz). The chemical shifts of C-6 and H-6 show that the configuration at this position of two isomers of **4b** is unchanged. The chemical shifts of the two isomers at C-4 have a 3.7 ppm difference, but in comparison with the unsubstituted *N*-3-benzyl-3-azabicyclo[3.2.0]heptane C-2 and C-4 (61.0) they are strongly shifted to a higher field, pointing to the presence of an *endo*-substituent at C-6. The influence of a C-2 substituent in the five-membered ring to C-4 shielding is of minor importance. $^{1}H-^{1}H$ spin−spin coupling between H-6 and H-5 (10−11 Hz) and between H-1 and H-7 (about 5 Hz) supports the assignment of *cis* orientation of H-5 and H-6 and *trans* orientation of H-1 and H-7, which corresponds to *exo* orientation of the C-7 substituent. In a recent review on the NMR spectroscopy of cyclobutanes,[18] limited outdated data on the coupling constants within a four-membered ring show that *cis* vicinal coupling constants are about 9 Hz, but *trans* coupling constants may be as low as 4.5 Hz and reach in some cases 10 Hz. This is understandable on the basis of the Karplus equation. The different *exo-endo* orientation in the two isomers of **4b** is also reflected on the C-7 ^{13}C chemical shifts; a high-field shift is caused by the 2-*endo* substituent, as usually observed in bicyclic systems.[19]

Table 3. NMR Data for 2-*Exo* and 2-*Endo* Isomers of **4b** (2-Methyl-3-benzyl-6-*endo*-carbethoxy-7-*exo*-diethylamino-3-azabicyclo-[3,2.1]heptane, $CDCl_3$, 800 MHz)



	2-*exo*-methyl derivative		2-*endo*-methyl derivative	
atom	^{1}H,mult, (*J*, Hz)	^{13}C	^{1}H,mult, (*J*, Hz)	^{13}C
1	2.28 (8.0, 5.0, 1.2)	47.7	2.51 (8.0, 5.4, 4.6)	45.1
2	2.91 (6.3q, 1.2)	62.5	2.33 (6.3q, 5.4)	61.7
4	2.57 (10.4, 6.9)	51.6	2.84 (10.7)	55.3
4	2.56 (10.4, 3.0)		1.90 (10.7, 6.8)	
5	2.99 m	34.1	2.87 m	32.8
6	3.02 (10, 7)	42.9	3.04 (11, 6.5)	43.3
7	3.50 (7, 5)	61.9	3.64 (11.2, 6.5, 4.6)	55.9
Me	0.93 (6.3)	13.2	1.18 (6.3)	11.2
Bn	3.68 (13.5)	55.0	4.08 (13.3)	56.8
Bn	3.67 (13.5)		2.92 (13.3)	
CO		172.8		172.7
OEt	4.06 (7.2)	60.1	4.06 (7.2)	60.0
OEt	1.15 (7.2)	14.2	1.05 (7.2)	14.1
NEt	2.57 (7.2)	41.7	2.57 (7.2)	41.5
NEt	1.02 (7.2)	10.5	1.05 (7.2)	10.9

In conclusion, we have found an efficient, one-step multicomponent reaction to yield the tetrasubstituted 3-azabicyclo[3.2.0]heptane derivatives. The obtained compounds are important pharmacophores or could be used as the starting material for the other N-containing heterocycles via ring fission. The investigation continues toward the asymmetric version of multicomponent coupling.

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Supporting Information Available: Experimental procedures and spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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