Organic LETTERS

Letter

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Synthesis of Tricyclic Benzazocines by Aza-Prins Reaction

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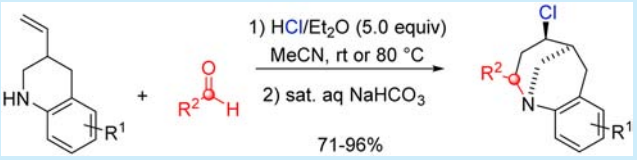
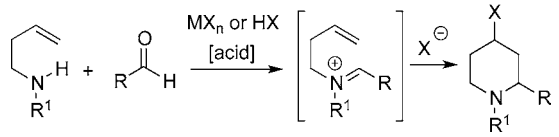
Supporting Information

ABSTRACT: The aza-Prins reaction of 3-vinyltetrahydroquinolines with aldehydes proceeded smoothly in the presence of hydrogen halides, and the tricyclic benzazocine derivatives were isolated in good to high yields. The reaction would proceed through the formation and cyclization of the iminium ion intermediate.



The aza-Prins reaction is an efficient method for the synthesis of piperidines.[1,2] The reaction frequently involves the condensation of an homoallylic amine with an aldehyde in the presence of an acid to give an iminium ion, which then undergoes the intramolecular nucleophilic attack by the olefin (Scheme 1). The wide applicability and usefulness of the aza-Prins reaction have been demonstrated by the synthesis of a variety of complex natural products.[3]

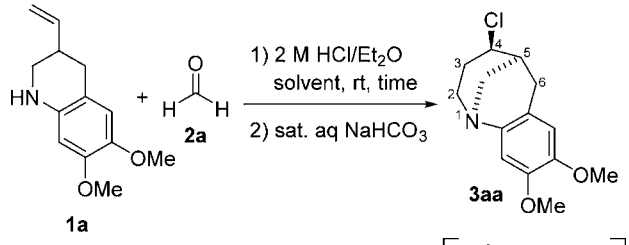
Scheme 1. Aza-Prins Reaction

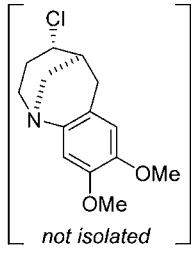


Recently, we developed the ring-expansion reaction of *N*-aryl-2-vinylazetidines and described a new method for the synthesis of tetrahydrobenzazocines.[4] During the study of the ring-expansion reaction, we found that the aza-Prins reaction of vinyltetrahydroquinolines with formaldehyde proceeded and tricyclic benzazocines, which have a very unique and pharmacologically attractive 1-azabicyclo[3.3.1]nonane skeleton,[5] were isolated. Herein we report the synthesis of tricyclic benzazocines by aza-Prins reaction.

We first explored the reaction of 6,7-dimethoxy-3-vinyl-1,2,3,4-tetrahydroquinoline **1a** with formaldehyde **2a**, employing an ethereal solution of hydrogen chloride. The results are summarized in Table 1. The aza-Prins reaction proceeded with 2.5 equiv of formaldehyde **2a** in the presence of 1.0 equiv of HCl for 5 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, and a tricyclic benzazocine **3aa** was isolated in 42% yield (entry 1). It is noteworthy that the reaction proceeded efficiently in the presence of a widely available and inexpensive acid (HCl). The regioselective formation of the 4,5-*trans* isomer was observed, and the 4,5-*cis* isomer was not isolated. The yield of **3aa** improved when the reaction was carried out in the presence of a larger amount of HCl; compound **3aa** was isolated in 82% yield when 3 equiv of HCl were added, and the yield of **3aa** reached 94% with 5 equiv of HCl (entries 2 and 3). We also examined the effect of the solvent on the reaction and found that acetonitrile[2a,6] was the best solvent. The reaction in acetonitrile completed in 1 h, and **3aa** was isolated in 96% yield (entry 4). When we used a smaller amount (1.5 equiv) of formaldehyde, the yield of **3aa** slightly decreased. Based on these results, the reaction conditions described in entry 4 were selected as the optimized conditions.

Table 1. Screening of Reaction Conditions





entry	HCl/Et_2O (equiv)	**2a**[a] (equiv)	solvent	time (h)	yield[b] (%)
1	1.0	2.5	CH_2Cl_2	5	42
2	3.0	2.5	CH_2Cl_2	5	82
3	5.0	2.5	CH_2Cl_2	5	94
4	5.0	2.5	MeCN	1	96
5	5.0	1.5	MeCN	1	90

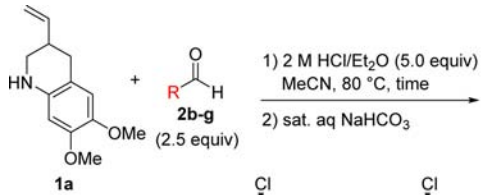
[a]Formalin (37% w/w) was used. [b]Isolated yield.

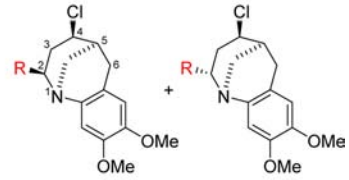
We next examined the reaction of **1a** with various aldehydes. The results are summarized in Table 2. The aza-Prins reaction of **1a** with acetaldehyde **2b** was sluggish at room temperature. The reaction, however, completed in 3.5 h at 80 °C, and the corresponding tricyclic benzazocine **3ab** was isolated in 81%

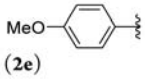
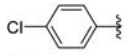
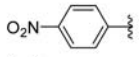
Received: November 30, 2016
Published: December 16, 2016

DOI: 10.1021/acs.orglett.6b03577
Org. Lett. 2017, 19, 266−269

Table 2. Aza-Prins Reaction of 1a with Various Aldehydes





entry	R	time (h)	product	yield[a] (%)	dr[b]
1	Me (**2b**)	3.5	**3ab**	81	1.8:1
2	Et (**2c**)	16	**3ac**	72	0.8:1
3	 (**2d**)	24	**3ad**	75	1.4:1
4	 (**2e**)	45	**3ae**	75	1.9:1
5	 (**2f**)	30	**3af**	86	1.4:1
6	 (**2g**)	14	**3ag**	86	1.5:1

[a]The combined yield of two isolated isomers. [b]The diastereomer ratio (2,4-*cis* isomer/2,4-*trans* isomer) was determined by ^{1}H NMR analysis of the crude sample.

yield (entry 1). In this reaction, the formation of two diastereomers was observed, which were isolated by column chromatography. The 2,4-*cis* isomer was formed as the major product, and a small amount of the 2,4-*trans* isomer was also isolated. No 4,5-*cis* isomer was isolated in this reaction. The reaction of **1a** with propanal **2c** completed after the reaction mixture was heated for 16 h at 80 °C, and **3ac** was isolated in 72% yield as a mixture of diastereomers (entry 2). The reaction of **1a** with aromatic aldehydes was successfully carried out, which enables the incorporation of aryl groups to the benzazocine framework. For example, the reaction of **1a** with benzaldehyde **2d** completed in 24 h, and the product (**3ad**) was isolated in 75% combined yield (entry 3). The reaction of **1a** with 4-methoxybenzaldehyde **2e** was more sluggish, and a longer reaction time was required (45 h, entry 4). The reactivity of 4-chlorobenzaldehyde **2f** was comparable to that of benzaldehyde, and the corresponding tricyclic benzazocine (**3af**) was isolated in 86% combined yield (entry 5). Compared to the reaction of **1a** with benzaldehyde, the reaction of **1a** with 4-nitrobenzaldehyde **2g** completed in a shorter period (14 h), and the products were isolated in good combined yield (entry 6). The structures of the products were confirmed by X-ray crystallographic analyses of *cis*- and *trans*-**3ad** (Figure 1). Reflecting the rigidity of the tricyclic system, the introduction of the phenyl group at the *cis* or *trans* position had little effect on the conformation of the two diastereomers.

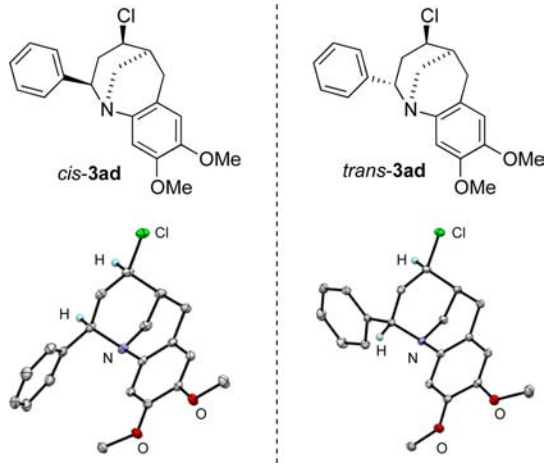
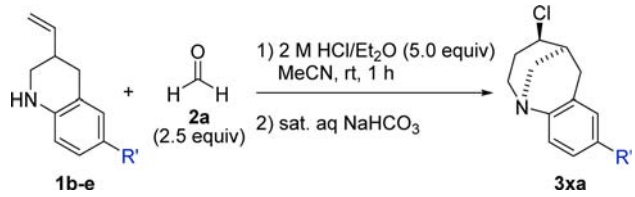


Figure 1. Crystal structures of *cis*- and *trans*-**3ad**.

In order to study the substituent effect on the reaction of vinyltetrahydroquinoline, the reactivity of a series of 6-substituted vinyltetrahydroquinolines was examined (Table 3).

Table 3. Aza-Prins Reaction of Various Vinyltetrahydroquinolines



entry	R′	product	yield[a] (%)
1	H (**1b**)	**3ba**	78
2	OMe (**1c**)	**3ca**	71
3	Me (**1d**)	**3da**	92
4	CF_3 (**1e**)	**3ea**	75

[a]Isolated yield.

The aza-Prins reaction of 3-vinyl-1,2,3,4-tetrahydroquinoline **1b** with **2a** proceeded smoothly, and the corresponding tricyclic product was isolated in 78% yield (entry 1). The 6-methoxy derivative **1c** and the 6-methyl derivative **1d** were suitable starting materials for this reaction (entries 2 and 3). Unexpectedly, the 6-trifluoromethyl derivative **1e**, which is a weaker nucleophile, was sufficiently reactive, and the tricyclic benzazocine was isolated in comparable yield (entry 4).

The substituent effect on the rate of the reaction was also studied by a competition experiment (Scheme 2). A mixture of 1.0 equiv each of **1b** and **1e** was treated with formaldehyde (1.0 equiv) in the presence of HCl (5.0 equiv), and the products were analyzed by ^{1}H NMR. The ratio of **3ba** to **3ea** was 1.0 to 0.88, indicating that compound **1b** was more reactive under the reaction conditions.

In order to expand the scope of this reaction, we examined the reaction of **1a** with **2a** in the presence of various hydrogen halides. The results are summarized in Table 4. Hydrochloric acid could be employed as the acid instead of the ethereal solution of HCl, and the product was isolated in an acceptable yield (69%, entry 1). Encouraged by this result, hydrobromic acid was employed for the reaction, and the corresponding bromide **3aa-Br** was isolated in 70% yield (entry 2). The iodide

DOI: 10.1021/acs.orglett.6b03577
Org. Lett. 2017, 19, 266−269

Scheme 2. Competition Experiment between 1b and 1e

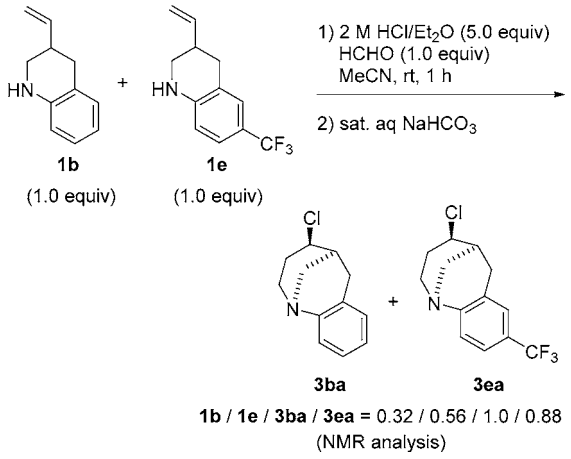
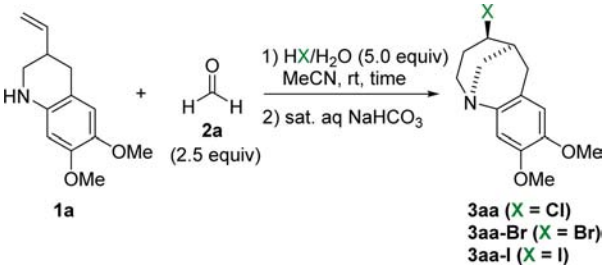


Table 4. Aza-Prins Reaction with Aqueous Hydrogen Halides



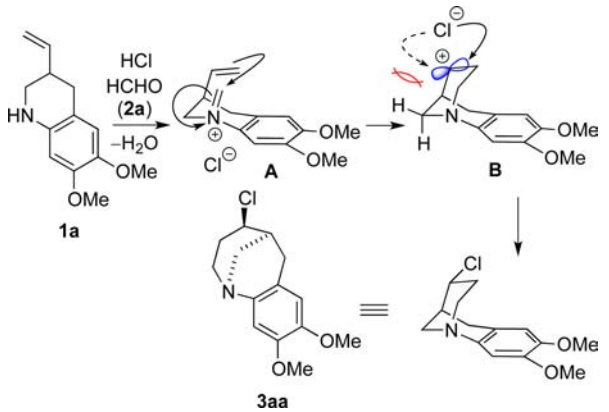
entry	acid	time (h)	product	yield[a] (%)
1	HCl/H_2O	1	**3aa**	69
2	HBr/H_2O	3	**3aa-Br**	70
3	HI/H_2O	4	**3aa-I**	82

[a]Isolated yield.

(**3aa-I**) was synthesized by the reaction of **1a**, **2a**, and hydroiodic acid (entry 3).[7]

A plausible mechanism of this reaction is shown in Scheme 3. Vinyltetrahydroquinoline **1a** would react with formaldehyde in

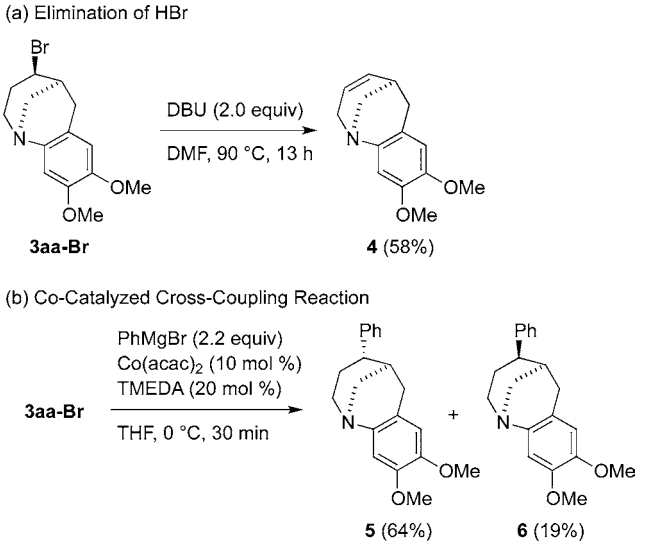
Scheme 3. A Plausible Mechanism



the presence of hydrogen chloride, and the iminium ion **A** would be generated. The cyclization of **A** would yield the carbocation **B**, which would be subsequently trapped by the chloride ion to form a tricyclic benzazocine **3aa**. Due to the steric hindrance of the bridging methylene group which was located in the vicinity of the carbocation, the chloride ion would approach the carbocation from the opposite side to the methylene group and the 4,5-*trans* isomer would be generated. The rate-determining step of this reaction would be the formation of the iminium ion **A**. A longer reaction time was required when an aldehyde with low electrophilicity (i.e., 4-methoxybenzaldehyde) was employed as the starting material (Table 2, entry 4). The result could be explained in terms of the reduced rate of the formation of the iminium ion **A**. The formation of **A** would proceed faster when a more nucleophilic quinoline was employed as the starting material (Scheme 2). The preferential formation of **3ba** in the competitive experiment supports the idea that the rate of the formation of **A** is the rate-determining step.

Finally, the utility of tricyclic benzazocines was demonstrated by studying the reactions of **3aa-Br** (Scheme 4). Elimination of

Scheme 4. Reactions of 3aa-Br



HBr proceeded when **3aa-Br** was treated with DBU at 90 °C for 13 h, and the olefin **4** was isolated in 58% yield. It is noteworthy that the single isomer was isolated in this reaction. The Co-catalyzed cross-coupling reaction[8] of **3aa-Br** with PhMgBr also proceeded smoothly to give **5** (64% yield) and **6** (19% yield).[9]

In summary, we synthesized tricyclic benzazocine derivatives by the aza-Prins reaction of vinyltetrahydroquinolines with aldehydes. The reaction proceeded under very simple reaction conditions, and the products were isolated in good to high yields. Our study provided a very concise method for the construction of the 1-azabicyclo[3.3.1]nonane skeleton. Further extension of the reaction to the synthesis of various *N*-heterocyclic compounds is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03577.

Detailed description of the experimental procedure and NMR spectra of new compounds (PDF)

X-ray data for *cis*-**3ad** (CIF)

X-ray data for *trans*-**3ad** (CIF)

X-ray data for **5** (CIF)

DOI: 10.1021/acs.orglett.6b03577
Org. Lett. 2017, 19, 266–269

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) For reviews, see: (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2012**, *16*, 1277.

(2) For recent examples, see: (a) Dobbs, A. P.; Guesne, S. J. J.; Parker, R. J.; Skidmore, J.; Stephenson, R. A.; Hursthouse, M. B. *Org. Biomol. Chem.* **2010**, *8*, 1064. (b) Yadav, J. S.; Subba Reddy, B. V.; Ramesh, K.; Narayana Kumar, G. G. K. S.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 818. (c) Launay, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, 41. (d) Sabitha, G.; Das, S. K.; Srinivas, R.; Yadav, J. S. *Helv. Chim. Acta* **2010**, *93*, 2023. (e) Yadav, J. S.; Reddy, B. V. S.; Ramesh, K.; Narayana Kumar, G. G. K. S.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 1578. (f) Reddy, B. V. S.; Borkar, P.; Chakravarthy, P. P.; Yadav, J. S.; Grée, R. *Tetrahedron Lett.* **2010**, *51*, 3412. (g) Subba Reddy, B. V.; Ramesh, K.; Ganesh, A. V.; Narayana Kumar, G. G. K. S.; Yadav, J. S.; Grée, R. *Tetrahedron Lett.* **2011**, *52*, 495. (h) Osawa, C.; Tateyama, M.; Miura, K.; Tayama, E.; Iwamoto, H.; Hasegawa, E. *Heterocycles* **2012**, *86*, 1211. (i) Clarisse, D.; Pelotier, B.; Fache, F. *Chem. - Eur. J.* **2013**, *19*, 857. (j) Taheri, A.; Quinn, R. J.; Krasavin, M. *Tetrahedron Lett.* **2014**, *55*, 5390. (k) Sun, Y.; Chen, P.; Zhang, D.; Baunach, M.; Hertweck, C.; Li, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 9012. (l) Nallasivam, J. L.; Fernandes, R. A. *Eur. J. Org. Chem.* **2015**, *2015*, 2012. (m) Okoromoba, O. E.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015**, *17*, 3975. (n) Chio, F. K. I.; Guesne, S. J. J.; Hassall, L.; McGuire, T.; Dobbs, A. P. *J. Org. Chem.* **2015**, *80*, 9868. (o) Durel, V.; Lalli, C.; Roisnel, T.; Weghe, P. *J. Org. Chem.* **2016**, *81*, 849. (p) Liu, G.-Q.; Cui, B.; Xu, R.; Li, Y.-M. *J. Org. Chem.* **2016**, *81*, 5144. (q) Ma, D.; Zhong, Z.; Liu, Z.; Zhang, M.; Xu, S.; Xu, D.; Song, D.; Xie, X.; She, X. *Org. Lett.* **2016**, *18*, 4328.

(3) For recent examples, see: (a) Altman, R. A.; Nilsson, B. L.; Overman, L. E.; Alaniz, J. R.; Rohde, J. M.; Taupin, V. *J. Org. Chem.* **2010**, *75*, 7519. (b) Reddy, B. V. S.; Chaya, D. N.; Yadav, J. S.; Grée, R. *Synthesis* **2012**, *2012*, 297. (c) Chen, Q.; Huo, X.; Yang, Z.; She, X. *Chem. - Asian J.* **2012**, *7*, 2543. (d) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3243. (e) Colin, O.; Greck, C.; Prim, D.; Thomassigny, C. *Eur. J. Org. Chem.* **2014**, *2014*, 7000.

(4) (a) Aoki, T.; Koya, S.; Yamasaki, R.; Saito, S. *Org. Lett.* **2012**, *14*, 4506. (b) Shimizu, T.; Koya, S.; Yamasaki, R.; Mutoh, Y.; Azumaya, I.; Katagiri, K.; Saito, S. *J. Org. Chem.* **2014**, *79*, 4367.

(5) (a) Mitsuhashi, K.; Shiotani, S.; Ohuchi, R.; Shiraki, K. *Chem. Pharm. Bull.* **1969**, *17*, 434. (b) Shaaban, M. A.; Ghoneim, K. M.; Kalifa, M. *Pharmazie* **1977**, *32*, 90.

(6) For the use of acetonitrile as a suitable solvent for the aza-Prins reaction, see: Dobbs, A. P.; Guesne, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880.

(7) When the reaction was carried out in the presence of TFA, the major product was assumed to be the hydroxylated product (**3aa-OH**). The analysis of the products has not been completed, since the purification of the products was difficult.

(8) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277.

(9) The structure of **5** was confirmed by X-ray crystallographic analysis. See the Supporting Information.

DOI: 10.1021/acs.orglett.6b03577
Org. Lett. 2017, 19, 266−269