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Intramolecular Aza-Piancatelli Rearrangement of Alkyl- or Arylamines Promoted by PPh_3/Diethyl Azodicarboxylate

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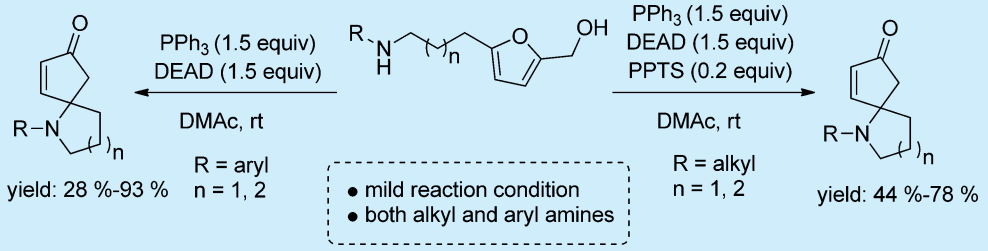
Supporting Information



ABSTRACT: A novel method for the construction of 1-azaspirocycles from 5-alkyl-/-arylamine furylcarbinols though intramolecular aza-Piancatelli rearrangement was developed. By using PPh_3/diethyl azodicarboxylate instead of a Lewis acid, 1-azaspirocyclic compounds were obtained in good yields and the reaction temperature was reduced to room temperature. In addition, substrates with groups that are sensitive to high temperatures or Lewis acids are tolerated under these reaction conditions. This is the first method that is applicable not only to 5-(*N*-arylaminoalkyl)furylcarbinols with better yields but also to 5-(*N*-alkylaminoalkyl)furylcarbinols.

The 1-azaspirocycle ring system is widely observed in natural products, such as histrionicotoxin,[1] cephalotaxine,[2] halichlorine,[3] stemonamine,[4] and erysotramidine[5] (Figure 1).

Many reactions have been developed to build this structural motif, and most of the synthetic strategies require two steps to separately build the tertiary carbon center and the spirocycle,[6] although few methods are able to construct this challenging framework via one-step routes. In 2011, Alaniz presented a novel cascade strategy for the formation of 1-azaspirocycles by applying the aza-Piancatelli rearrangement. This reaction is simple and inexpensive and can be applied to many different arylamines with high yields; however, no alkylamines have been used.[7] In the following years, Alaniz reported similar reactions, including intramolecular Piancatelli rearrangement of alcohols and donor−acceptor cyclopropanes.[8,9] When substrates with hydroxylamine were attempted, the structural motif was obtained in high yields, but the cleavage of N−O bonds failed using the traditional methods.[10] Here, we present the first intramolecular aza-Piancatelli rearrangement of alkylamines, and this protocol can also be applied to arylamines with better yields (Scheme 1). Thus, we can avoid the cleavage of C−N or

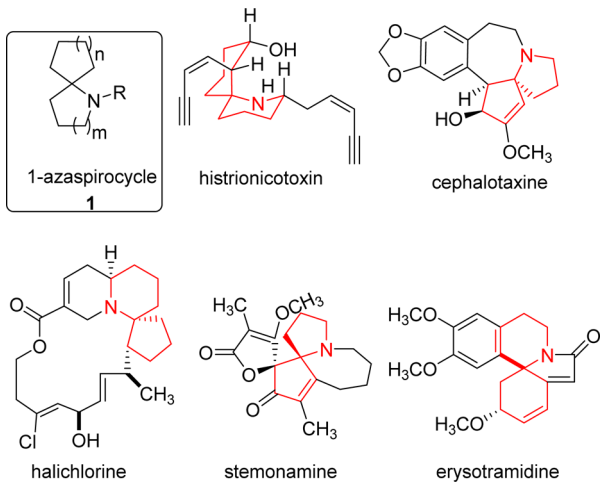
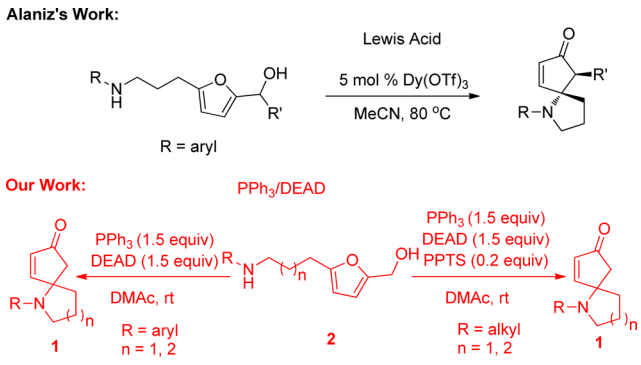


Figure 1. Natural products with 1-azaspirocycle ring systems.

Scheme 1. Intramolecular Aza-Piancatelli Rearrangement



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Scheme 2. Synthetic Routes of Furylcarbinols

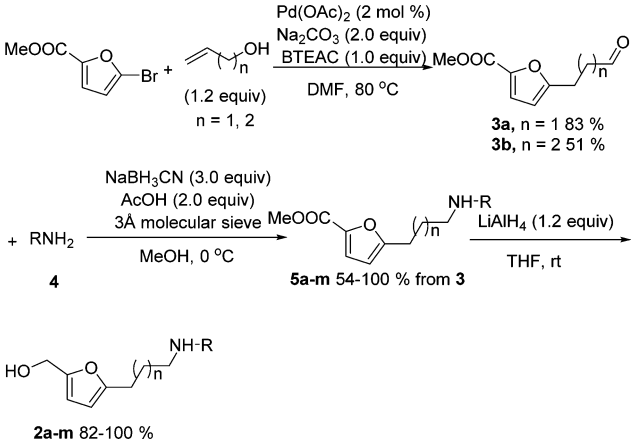
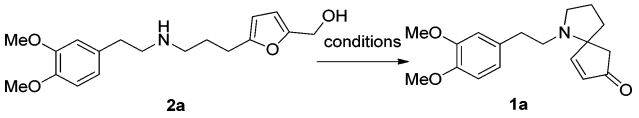


Table 1. Studies of the Intramolecular Aza-Piancatelli Rearrangement Reaction Conditions



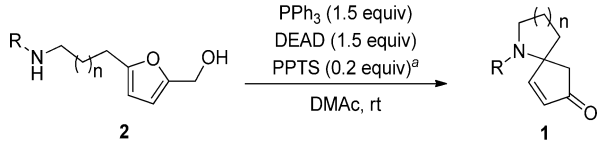
entry	promoter (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	$Dy(OTf)_3$ (0.05)	CH_3CN	80	36	nr
2	$Dy(OTf)_3$ (0.05), $TsOH•H_2O$ (1.00)	CH_3CN	80	36	nr
3	$ZnCl_2$ (0.05)	DME/H_2O (1:1)	100	2	nr
4	PPh_3 (1.20) DEAD (1.20)	THF	0 to rt	24	28
5	ADDP[b] (1.50) Bu_3P (1.50)	benzene	50	8	nr
6	PPh_3 (1.20) CCl_4 (1.20) TEA (1.20)	DMF	0 to rt	12	nr
7	PPh_3 (1.30) NBS (1.20) TEA (1.20)	DCM	0 to rt	12	nr
8	PPh_3 (1.50) DEAD[c] (1.50)	DMF	0 to rt	3	48
9	PPh_3 (1.50) DEAD (1.50)	DMAc	0 to rt	2	70
10	PPh_3 (1.50) DEAD (1.50)	CH_3CN	rt	3	40
11	PPh_3 (1.50) DEAD (1.50)	DCM	rt	3	24
12	PPh_3 (1.50.) DEAD (1.50)	DMSO	rt	3	20
13	PPh_3 (1.50) DEAD (1.50) PPTS[d] (0.20)	DMAc	rt	0.5	78

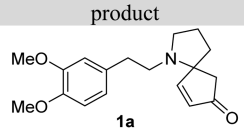
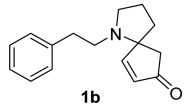
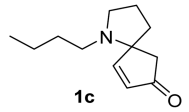
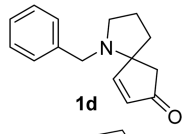
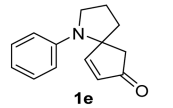
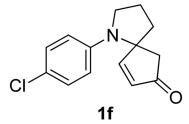
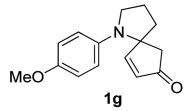
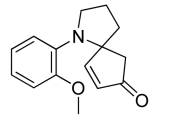
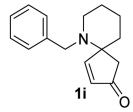
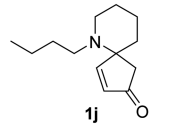
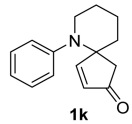
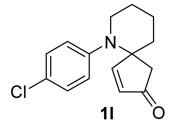
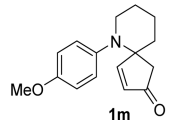
[a]Isolated yield. [b]ADDP = 1,1′-(azodicarbonyl)dipiperidine. [c]DEAD = diethyl azodicarboxylate. [d]PPTS = pyridinium toluene-4-sulfonate.

O−N bonds by introducing the group we need to connect with the N atom first, simplifying the synthetic route.

All of the furylcarbinols were synthesized using standard synthetic procedures (Scheme 2): methyl 5-bromo-2-furoate was used as the starting material, and one Heck reaction step then provided the aldehyde **3**. After condensation with amine **4**

Table 2. Studies on Intramolecular Aza-Piancatelli Rearrangement



entry	time (h)	product	yield (%)[b]
1	0.5	 1a	78
2	0.5	 1b	72
3	0.5	 1c	71
4	0.5	 1d	72
5	0.5	 1e	83
6	0.5	 1f	93
7	0.5	 1g	89
8	0.5	 1h	88
9	12	 1i	45
10	12	 1j	44
11	12	 1k	28
12	12	 1l	42
13	12	 1m	35

[a]Added when R is an alkyl group. [b]Isolated yield.

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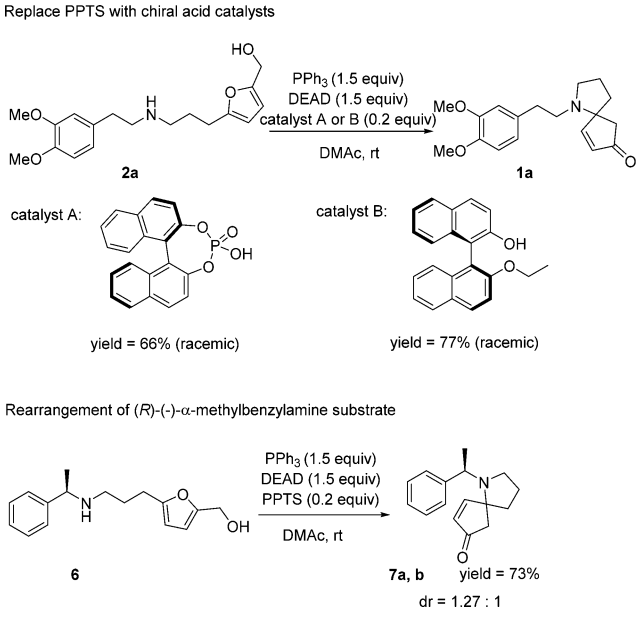
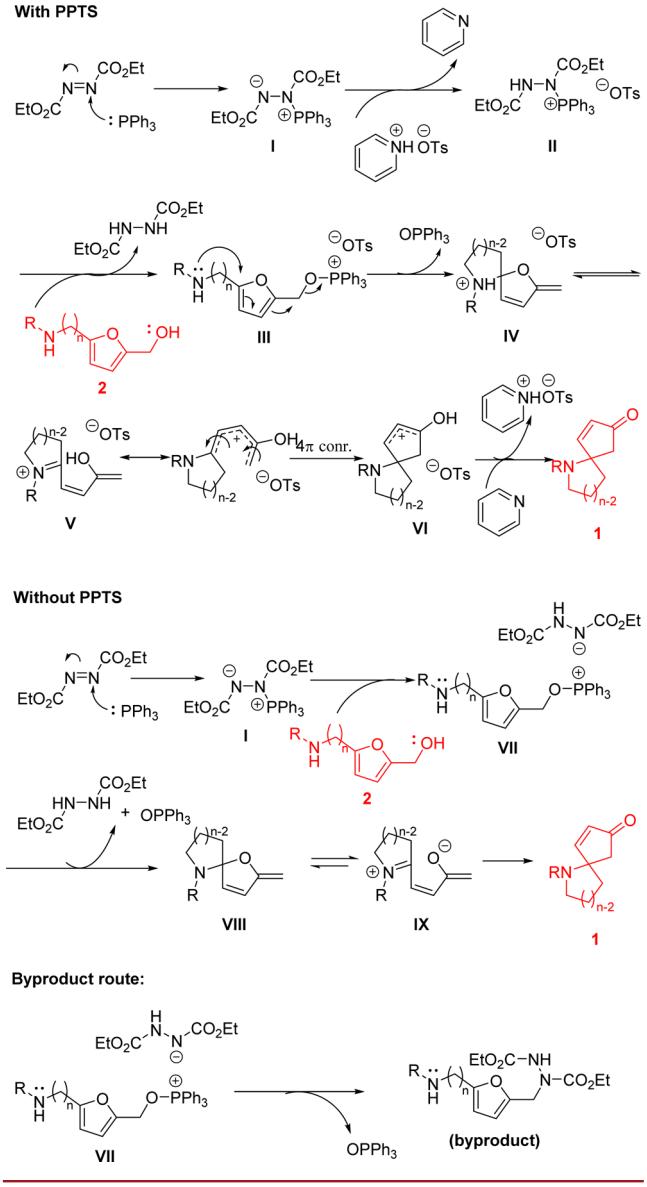
Scheme 3. Studies of the Chiral Aza-Piancatelli Rearrangement



Scheme 4. Proposed Mechanism for Intramolecular Aza-Piancatelli Rearrangement



and a Borch reaction, we obtained amine **5**, which was then reduced by $LiAlH_4$ to yield furylcarbinol **2**.

Furylcarbinol **2a** was selected as a model substrate. Because no aza-Piancatelli rearrangement of alkylamine furylcarbinols have been reported, we first tried the Lewis acid $Dy(OTf)_3$, $Dy(OTf)_3$/TsOH, or $ZnCl_2$ as the catalyst, but no product was detected (Table 1, entries 1−3). Perhaps the strong Lewis basicity of the alkylamines could poison the Lewis acids. We turned our attention to nonacidic conditions to promote leaving of the hydroxyl group, which is considered to be the start of the aza-Piancatelli rearrangement. After attempting several conditions, such as PPh_3/DEAD,[11] *n*-Bu_3P/ADDP,[12] PPh_3/CCl_4/TEA, and PPh_3/NBS/TEA (Table 1, entries 4−7),[13,14] we successfully isolated the aza-Piancatelli rearrangement product in 28% yield using the PPh_3/DEAD/THF system. We then screened several solvents, including DMF, DMAc, CH_3CN, DCM, and DMSO (Table 1, entries 8−12). DMAc was found to be the best, possibly because DMAc is favorable for proton migration, which is very important in the rearrangement process. When a catalytic amount of PPTS was added for the alkylamine substrates, the yield could be further improved (Table 1, entry 13).

The scope of the aza-Piancatelli rearrangement was investigated. For the synthesis of 1-azaspiro[4.4]nonanes from alkylamines, we chose several R groups, such as phenylethyl, *n*-butyl, or benzyl. The yields ranged from 71 to 78% (Table 2, entries 1−4). For the synthesis of 1-azaspiro[4.4]nonanes from arylamines, the yields were much better, regardless of whether the substituent was electron-withdrawing or electron-donating (Table 2, entries 5−8). Moving the methoxyl group from the para position to the ortho position had little influence on the yields (Table 2, entries 7 and 8). When we applied this method to construction of the 6-azaspiro[4.5]decane ring system, the yields decreased substantially for both the alkylamine substrates and the aromatic amine substrates. We suggest that the large ring strain of the six-membered heterocycle restricted the aza-Piancatelli arrangement. For the alkylamine substrates, the yields were approximately 45% (Table 2, entries 9 and 10), and for aromatic amine substrates, the yields ranged from 28 to 42% (Table 2, entries 11−13). The yields of the alkylamine substrates were higher than those of the aromatic amine substrates, which was opposite the result for the 1-azaspiro[4.4]nonanes. When there were substituents in the benzene ring of the arylamine substrates, the yields were higher, which was consistent with the results for the 1-azaspiro[4.4]-nonanes.

Furylcarbinol **2a** was chosen as model to study the chiral aza-Piancatelli rearrangement (Scheme 3y clearan). We tried to replace the PPTS with chiral acid catalysts, such as catalyst (*R*)-(−)-1,1′-Binaphthyl-2,2′-diylhydrogen phosphate **A** or catalyst (*S*)-2′-Ethoxy-1,1′-binaphthalen-2-ol **B**. Only racemic product was obtained. The rearrangement of furylcarbinol **6** using (*R*)-(−)-α-methylbenzylamine as chiral auxiliary occurred with little control of stereoselectivity.

The proposed mechanism is analogous to the intramolecular aza-Piancatelli rearrangement catalyzed by a Lewis acid,[7] except for the leaving method of the hydroxyl group. The proposed

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mechanism is described in Scheme 4: PPh_3 reacts with DEAD to form intermediate **I**, which is consistent with the Mitsunobu reaction. Intermediate **I** acquires a proton from PPTS to form intermediate **II**, which is then attracted by substrate **2** to form intermediate **III**. Intermediate **III** undergoes molecular rearrangement to form intermediate **IV**, which then converts to **V**. Intermediate **V** undergoes Nazarov rearrangement, yielding intermediate **VI**, which produces the desired product **1** after deprotonation. Without PPTS, intermediate **I** obtained a proton from compound **2**, formed intermediate **VII**, and rearranged to intermediate **VIII**, after ring open and ring close, to yield the product **1**. The byproduct is formed though the leaving the $OPPh_3$ of intermediate **VII**. PPTS can transform a proton to intermeditate **I** and, thus, form intermediate **III** instead of intermediate **VII**. In this way, the byproduct route is depressed. What's more, the transformation from intermediate **IV** to intermediate **V** is easier than the transformation from intermediate **VIII** to intermediate **IX**, and the rate of aza-Piancatelli rearrangement is increased.

In conclusion, we have developed an intramolecular aza-Piancatelli rearrangement that is suitable for both alkyl- and arylamine furylcarbinols. This is the first report of the aza-Piancatelli rearrangement of alkylamines; thus, the cleaving of C−N bonds for arylamines or N−O bonds for hydroxylamine can be avoided. The reaction is promoted by PPh_3/DEAD for arylamine furylcarbinols and PPh_3/DEAD/PPTS for alkylamine furylcarbinols at room temperature. Because it proceeds without Lewis acids or high temperatures, this reaction is expected to be tolerant to acid-sensitive substrates or substrates that decompose at high temperatures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03853.

Full experimental details, spectroscopic data, and ^1H and ^{13}C NMR spectra for the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U. S. A.* **1971**, *68*, 1870−1875.
(2) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194−2197.
(3) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867−3870.
(4) (a) Iizuka, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1973**, 125−126. (b) Ye, Y.; Qin, G.-W.; Xu, R.-S. *J. Nat. Prod.* **1994**, *57*, 665−669.
(5) Ito, K.; Suzuki, F.; Haruna, M. *J. Chem. Soc., Chem. Commun.* **1978**, 733−734.
(6) Dake, G. *Tetrahedron* **2006**, *62*, 3467−3492.
(7) Palmer, L. I.; Alaniz, J. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 7167−7170.
(8) Palmer, L. I.; Read de Alaniz, J. R. *Org. Lett.* **2013**, *15*, 476−479.
(9) Wenz, D. R.; Read de Alaniz, J. R. *Org. Lett.* **2013**, *15*, 3250−3253.
(10) Veits, G. K.; Wenz, D. R.; Palmer, L. I.; Amant, A. S.; Hein, J. E.; Alaniz, J. R. *Org. Biomol. Chem.* **2015**, *13*, 8465−8469.
(11) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1−28.
(12) Boger, D. L.; Mckie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1996**, *118*, 2301−2302.
(13) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801−811.
(14) Schmida, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiserb, H. *Helv. Chim. Acta* **1990**, *73*, 1276−1299.

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