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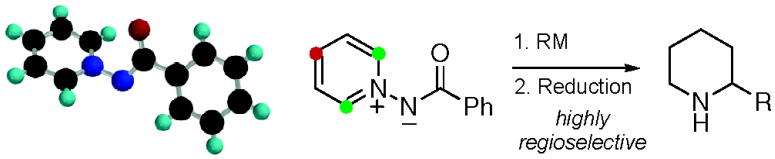

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Complexation Promoted Additions to *N*-Benzoyliminopyridinium Ylides. A Novel and Highly Regioselective Approach to Polysubstituted Piperidines

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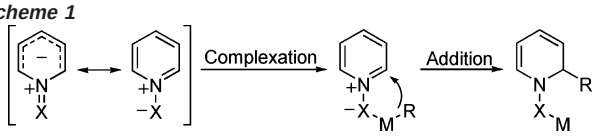
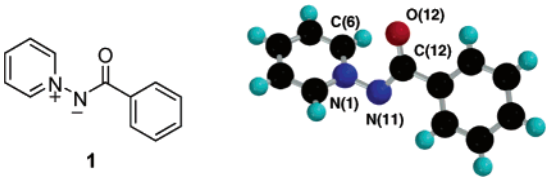
The piperidine unit is widely found in many natural products and biologically important pharmaceuticals. Extensive reviews describing various strategies for their syntheses and their natural occurrence have been published.[1,2] One of the most expedient methods to access piperidine subunits has been through addition reactions of nucleophilic reagents to an activated pyridinium moiety. However, this approach is complicated by the multiple electrophilic sites on the ring which generally translate into nonregioselective nucleophilic additions. One way to circumvent this problem is through the use of protecting groups to block undesired electrophilic sites, a methodology that has been exploited by Comins.[3] Another approach involves the use of a directing group, allowing for controlled addition to the 2 position. Pioneering work using this strategy has been reported by Marazano.[4] Recent work in our group has led to the development of a new system for the regio- and stereoselective synthesis of 2-substituted dihydropyridines and piperidines.[5] While these systems favor the regioselective addition of various nucleophiles to the 2 position, the limitations of this methodology include the incompatibility of 2-substituted pyridine toward the activation conditions and poor regiocontrol with bulky aliphatic and benzylic organometallic reagents. Herein, we report a novel and highly regioselective approach to 2- and 2,6-disubstituted tetrahydropyridines from unsubstituted and 2-substituted pyridinium moieties using *N*-benzoyliminopyridinium ylides.

All of the current successful systems rely on classical pyridinium salts, having a dissociated counterion. This anion can serve as a Lewis base to activate the organometallic nucleophile, making the directing group on the pyridinium salt less effective. Conversely, the ylides have the counterion directly linked to the pyridinium moiety, and our postulate was that this counterion could serve both as a Lewis base and as a directing group for the nucleophile. Furthermore, an uncomplexed pyridinium ylide should possess a lower electrophilicity due to the delocalization of the negative charge in the pyridine ring. The complexation of the nucleophile should enhance the electrophilicity of the ring, thus promoting the addition (Scheme 1).

Scheme 1



Our selection for the nature of X (Scheme 1) was based upon the N−X bond strength and its directing ability. Also, following addition, it is desirable that the N−X bond be easily cleaved, affording the desired piperidines. Pyridine *N*-oxide was not considered a suitable candidate due to a variety of reports showing rearrangements following addition of a nucleophile.[6] Instead, we focused on *N*-iminopyridinium ylides (X = NR), where modifications of R could tune the reactivity of the pyridinium moiety.



1

Figure 1. X-ray crystal structure of **1**. Selected bond lengths [Å] and angles [deg]: C(12)−O(12) 1.247, C(12)−N(11) 1.335, N(1)−N(11)−C(12) 115.5, C(6)−N(1)−N(11)−C(12), 59.3.

Compounds of this type have been used in various rearrangements leading to novel heterocyclic compounds.[7,8]

An extensive study of the nature of the substituent on the exocyclic nitrogen established that the use of a benzoyl group was optimal. *N*-Benzoyliminopyridinium ylide (NAPBz) **1** is rapidly synthesized in excellent yield by benzoylation of the commercially available *N*-aminopyridinium iodide.[9] The *N*-aminopyridinium salts can also be prepared by direct amination of the corresponding pyridine, encompassing a wide variety of pyridines, including 2-substituted ones.[10,11] NAPBz shows interesting physical and spectroscopic properties.[12] The IR spectrum shows the carbonyl stretching band at 1560 cm^{-1}. This value is about 90 cm^{-1} lower than a corresponding hydrazide. This provides strong evidence for the delocalization of the negative charge into the carbonyl. Further proof of this is illustrated by the X-ray crystal structure of **1** (Figure 1) with a C−O bond length of 1.247 Å, as compared to the corresponding hydrazide (1.219 Å, see Supporting Information).[13]

Several Grignard reagents were then added to **1**, and these results are summarized in Table 1. The addition proceeds smoothly at room temperature within 25 min. Because the dihydropyridines obtained were found to be unstable, they were reduced in situ with a methanolic solution of $NaBH_4$ to afford the 1,2,5,6-tetrahydropyridines in good to excellent yields. The level of regiocontrol was excellent (>95:5), favoring the 1,2-adduct. Particular attention should be given to entries 4, 5, 7, and 8, which are known to be problematic, usually giving predominant 1,4-addition. To our surprise, even the addition of *t*-BuMgCl (entry 5), a typical reagent for 1,4-addition,[14] gave a modest amount of the 1,2-adduct. Last, and most importantly, is the high regioselectivity obtained in the addition of a benzylic Grignard. It has been shown by Marazano to be a reagent selective for 1,4-addition.[4a]

This methodology can also be applied to 2-substituted pyridines. There are reports of electrophilic activation of the former followed by addition of a nucleophile; however, the addition is nondirected and usually results in a mixture of regioisomers.[15] Several Grignard reagents were added to the 2-methyl-*N*-benzoyliminopyridinium ylide **4**, and the results are summarized in Table 2.

In all cases, the regioselectivity was complete, favoring the 1,2-adduct. Following the addition, the resulting dihydropyridines were reduced to afford the 2,6-disubstituted tetrahydropyridines, favoring the cis isomer in moderate to excellent diastereoselectivities and

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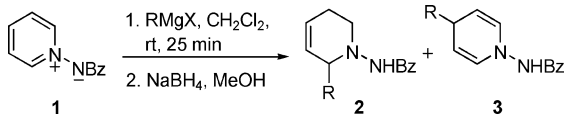
Table 1. Formation of 1,2,5,6-Tetrahydropyridines[a]

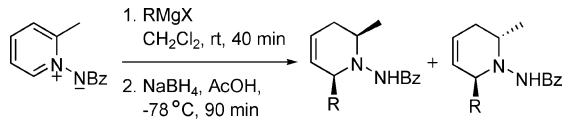


1 2 3

entry	RMgX	2/3	yield (%)	products
1	MeMgBr	>95/5	91	**2a**
2	EtMgBr	>95/5	83	**2b**
3	*n*-PrMgCl	>95/5	87	**2c**
4	*i*-PrMgBr	>95/5	81	**2d**
5	*t*-BuMgCl	43/57	39, 28	**2e**, **3e**
6	VinylMgBr	>95/5	77	**2f**
7	AllylMgBr	>95/5	79	**2g**
8	BnMgCl	93/7	71	**2h**
9	BnMgCl	>95/5	85	**2h**

[a] See Supporting Information for details.

Table 2. Formation of 2,6-Disubstituted 1,2,5,6-Tetrahydropyridines

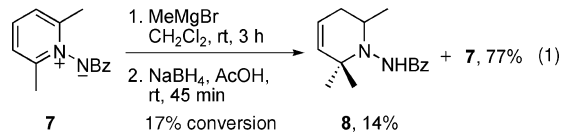


4 5 6

entry	RMgX	5/6[a]	yield (%)[b]	products
1	MeMgBr	69/31	86	**5a**, **6a**
2	*n*-PrMgCl	81/19	85(61)	**5b**, **6b**
3	*i*-PrMgBr	>95/5	84(84)	**5c**

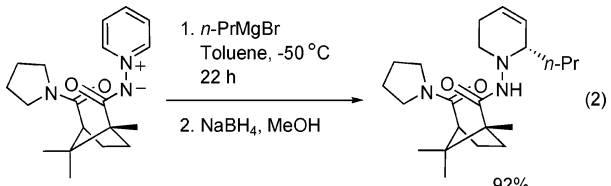
[a] Ratios were determined by ^{1}H NMR. [b] Combined yields of the two diastereomers. Isolated yield of the cis isomer is shown in parentheses.

in high yields. Even addition to 2,6-disubstituted pyridinium ylide showed complete 1,2-regioselectivity (eq 1). The preference for generating a quaternary center in the 2 position is unprecedented and shows the strong directing ability of these pyridinium ylides.



7 17% conversion 8, 14%

Raney Nickel was shown to efficiently cleave the N−N bond, giving access to the corresponding piperidines.[16] It was also possible to cleave the N−N bond while preserving olefin functionalities using lithium in ammonia.[17] Preliminary results of a diastereoselective system are encouraging. The addition of *n*-PrMgBr to chiral pyridinium ylide **9** resulted in complete regioselectivity in the 2 position, providing the tetrahydropyridine **10** in 92% yield and 84:16 dr (eq 2).



9 10 92% 84:16 *d.r.*

In conclusion, we have shown that *N*-benzoyliminopyridinium ylides are promising substrates for the synthesis of polysubstituted piperidines, showing an unprecedented reactivity. The development of an enantioselective version leading to nonracemic piperidines is also currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data of selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Piperidine: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862−2892.
(2) Indolizidine/quinolizidine: Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520−542.
(3) (a) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651−2652. (b) Comins, D. L.; Zhang, Y. *J. Am. Chem. Soc.* **1996**, *118*, 12248−12249. (c) Comins, D. L.; Guerra-Weltzien, L. *Tetrahedron Lett.* **1996**, *37*, 3807−3811. (d) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719−4728.
(4) (a) Guilloteau-Bertin, B.; Compère, D.; Gil, L.; Marazano, C.; Das, B. C. *Eur. J. Org. Chem.* **2000**, 1391−1399. (b) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052−2057.
(5) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.
(6) (a) Schiess, P.; Monnier, C.; Ringele, P.; Sendi, E. *Helv. Chim. Acta* **1974**, *57*, 1676−1691. (b) Van Bergen, T. J.; Kellogg, R. M. *J. Org. Chem.* **1971**, *36*, 1705−1708.
(7) (a) Tamura, Y.; Ikeda, M. *Adv. Heterocycl. Chem.* **1981**, *29*, 71−137. (b) Timpe, H. J. *Adv. Heterocycl. Chem.* **1974**, *17*, 213−253.
(8) (a) Yeung, J. M.; Corleto, L. A.; Knaus, E. E. *J. Med. Chem.* **1982**, *25*, 191−195. (b) Yeung, J. M.; Corleto, L. A.; Knaus, E. E. *J. Med. Chem.* **1982**, *25*, 720−723. (c) Knaus, E. E.; Redda, K. *J. Heterocycl. Chem.* **1976**, *13*, 1237−1240.
(9) *N*-Aminopyridinium iodide is commercially available through Lancaster.
(10) Gösl, R.; Meuwsen, A. *Org. Synth.* **1963**, *43*, 1.
(11) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1−17.
(12) NAPBz is a white nonhygroscopic crystalline solid which can be kept for months on the workbench without any noticeable decomposition.
(13) For an extended structural analysis of **1**, see Supporting Information.
(14) Holm, T. *Acta Chem. Scand.* **1991**, *45*, 276−279.
(15) (a) Brana, M. F.; Morán, M.; Pérez de Vega, M. J.; Pita-Romero, I. *J. Org. Chem.* **1996**, *61*, 1369−1374. (b) Brana, M. F.; Morán, M.; Pérez de Vega, M. J.; Pita-Romero, I. *Tetrahedron Lett.* **1994**, *35*, 8655−8658. (c) Krow, G. R.; Lee, Y. B.; Raghavachari, R.; Szczepanski, S. W. *Tetrahedron* **1991**, *47*, 8499−8514. (d) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1988**, *53*, 3507−3512. (e) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094−2096. (f) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215−222. (g) Krow, G. R.; Cannon, K. C.; Carey, J. T.; Lee, Y. B.; Szczepanski, S. W. *J. Heterocycl. Chem.* **1985**, *22*, 131−135. (h) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1985**, *50*, 287−288. (i) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1984**, *25*, 3297−3300.
(16) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Dupont-Feneau, J.; Declercq, J. P. *Synthesis* **1995**, 1038−1050. Treatment of **5b** with HCl/Et_2O afforded (±)-*cis*-2-methyl-6-propylpiperidine hydrochloride **11** (91%).
(17) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219−6223. By applying these conditions to **2g** followed by in situ trapping with benzyl chloroformate, we isolated the corresponding CBz protected tetrahydropyridine in 87% yield.

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