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Lewis Acid-Mediated S_N2 Type Displacement by Grignard Reagents on Chiral Perhydropyrido[2,1-*b*]pyrrolo[1,2-*d*][1,3,4]oxadiazine. Chirality Induction in Asymmetric Synthesis of 2-Substituted Piperidines

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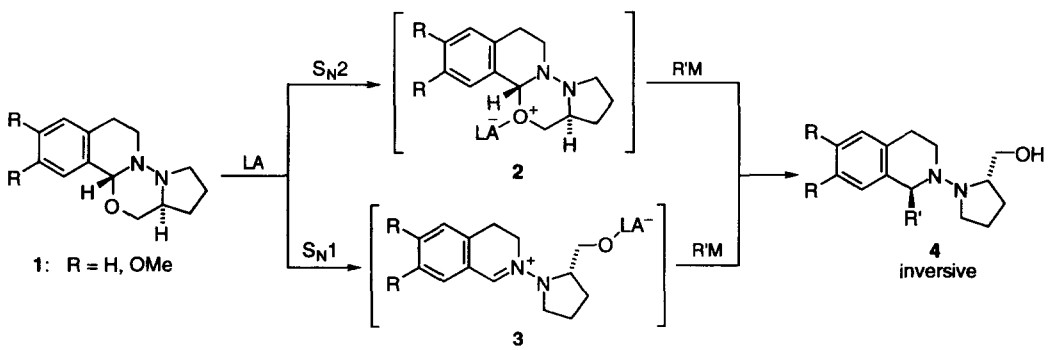
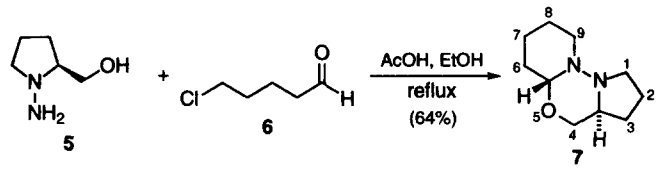
Abstract: Et_2AlCl-mediated nucleophilic alkylation with Grignard reagents on chiral perhydropyrido[2,1-*b*]pyrrolo[1,2-*d*][1,3,4]oxadiazine has proved to proceed via an S_N2 mechanism at low temperatures (below −80 °C) with high to excellent inversive stereoselection, while, at an elevated temperature, hydrazonium ions are formed preferentially leading to retentive stereoselection. This methodology provides useful access to enantioselective preparation of 2-substituted piperidines and is used for asymmetric synthesis of (+)-coniine. © 1997 Elsevier Science Ltd.

The diversity of selectivities involving mechanisms either via ionization (S_N1) or displacement (S_N2) in nucleophilic substitution on N,O-acetals is a subject of current interest.[1] In connection with this and our program to explore the use of N,O-acetals in asymmetric synthesis, we have recently reported[2] the Lewis acid-mediated asymmetric alkylation of the hydrazine N,O-acetals **1** with organometallic reagents. In this series, nucleophilic substitution occurred with excellent inversive selection affording the 1-substituted isoquinolines **4**, in which, however, the mechanistic aspect of the reaction pathway, that is, via either direct nucleophilic displacement on a Lewis acid complex **2** (S_N2), or Lewis acid-induced ionization to a hydrazonium ion pair **3** (S_N1) has remained unclear. As an extension of the synthetic utility of this asymmetric alkylation using the hydrazine N,O-acetals, we were prompted to investigate the possibility of enantioselective synthesis of 2-substituted piperidines and obtain a better understanding of the mechanistic aspect of the nucleophilic hydrazine N,O-acetal substitution. In this paper, we wish to describe our experimental results on Lewis acid-mediated nucleophilic alkylation of (3a*S*,5a*R*)-perhydropyrido[2,1-*b*]pyrrolo[1,2-*d*][1,3,4]oxadiazine (**7**) which indicate a mechanistic divergence; the reaction can predominantly occur by an S_N2 or S_N1 mechanism providing inversive or retentive stereoselectivities, respectively, depending on reaction temperature.



The required chiral tricyclic 1,3,4-oxadiazinane **7** was readily available in 64% yield as a single diastereomer by treating (*S*)-1-amino-2-pyrrolidinemethanol (**5**) with 5-chloropentanal (**6**) and acetic acid in ethanol at reflux. The configuration of the newly generated stereogenic center C-5a in **7** was assigned by ^{1}H NMR NOESY experiments (Figure 1), which verifies the stereochemistry of the 9a-N and 9b-N centers to be syn in accord with conformational preference based on "gauche attractive effect",[3] thus proving the fused tricyclic ring system of **7** to be *cis-syn-trans*.



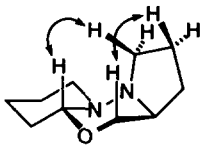
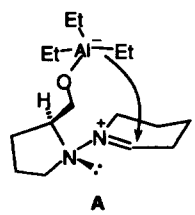
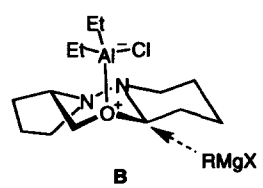


Figure 1. Selected NOEs of **7**.

At first, we examined alkylation of **7** with Et_3Al in chloroform at room temperature (20 °C), which showed 96:4 retentive stereoselection (Table 1, entry 1) rationalized by invoking a hydrazonium ion pair **A** undergoing internal alkyl delivery from the upper face in agreement with the previous explanation for the retentive selectivity with the isoquinoline series,[2] though the reaction was slow to recover a considerable amount (44%) of the starting material. When the Grignard reagents PrMgBr and $PhCH_2MgCl$ in THF were employed at room temperature, an inversive tendency was seen (entries 2 and 3), albeit in low selectivities (68:32 and 58:42, respectively). These results indicate that, in comparison with Et_3Al which sufficiently activates the N,O-acetal to cleave the C—O bond leading to the hydrazonium ion, the Grignard reagents with lower Lewis acidity[5] are less reactive for C—O bond cleavage and, thus, direct alkoxy displacement (S_N2) leading to the inversive products **8b** and **8d** slightly predominated over the hydrazonium ion pathway with stereoretention to give **9b** and **9d**. In anticipation of preventing the formation of the hydrazonium ion to obtain enhanced inversive S_N2 selectivity, **7** was treated with the Grignard reagent, PrMgBr, at low temperature (–85 °C); however, the reaction was very sluggish resulting in no alkylation (entry 7).

These results suggest that a stronger Lewis acid with a less nucleophilic alkyl group is necessary at low temperature that would allow the initial coordination of the N,O-acetal oxygen with the Lewis acid to facilitate the subsequent nucleophilic attack by the Grignard reagents. Thus, **7** was treated with the Grignard reagents in the presence of Et_2AlCl at –15 °C. As recognized from the results in entries 4–6, Et_2AlCl, acting as a Lewis acid, rendered the substrate sufficiently reactive toward the Grignard reagents at low temperature; in the case with BuMgCl the reaction proceeded with the inversive stereoselection, albeit in a modest selectivity (70:30), in agreement with an S_N2 mechanism as illustrated by **B**. However, in the cases with PrMgBr and $PhCH_2MgCl$, the stereoselection was changed to a retentive manner with low selectivities (65:35 and 53:47, respectively), indicating that an S_N1 substitution pathway proceeding probably via the hydrazonium ion **C** is slightly favored over that proceeding via the S_N2 mechanism (**B**) at –15 °C. Thus, for the S_N2 pathway it is requisite that the formation of the hydrazonium ion (**C**) is slower than the nucleophilic attack on the oxonium ion (**B**). Thus, the Et_2AlCl-mediated substitution with the Grignard reagents was conducted below –80 °C and the results are presented in Table 1 (entries 8–12). As can be seen in the table, the inversive stereoselection was observed in all cases with remarkably enhanced selectivity, especially in the cases of using the butyl and benzyl Grignard





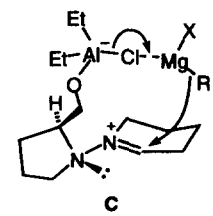
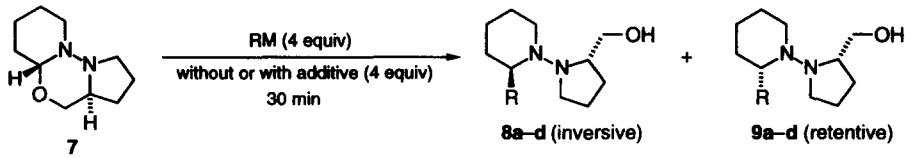


Table 1. Nucleophilic Alkylation of Hydrazine N,O-Acetal 7[a]



Entry	RM	Additive	Solvent	Temp	Products	Ratio[b]	Yield (%)[c]
1	Et_3Al	none	$CHCl_3$	rt	**8a/9a**	4 : 96	21[d]
2	PrMgBr	none	THF	rt	**8b/9b**	68 : 32	75
3	$PhCH_2MgCl$	none	THF	rt	**8d/9d**	58 : 42	81
4	PrMgBr	Et_2AlCl	THF	–15 °C	**8b/9b**	35 : 65	52
5	BuMgCl	Et_2AlCl	THF	–15 °C	**8c/9c**	70 : 30	43
6	$PhCH_2MgCl$	Et_2AlCl	THF	–15 °C	**8d/9d**	47 : 53	47
7	PrMgBr	none	THF	–85 °C	no reaction		
8	EtMgBr	Et_2AlCl	THF	–85 °C	**8a/9a**	82 : 18	73
9	PrMgBr	Et_2AlCl	THF	–80 °C	**8b/9b**	91 : 9	72
10	PrMgBr	Et_2AlCl	THF	–90 °C	**8b/9b**	95 : 5	84
11	BuMgCl	Et_2AlCl	THF	–85 °C	**8c/9c**	99 : 1	82
12	$PhCH_2MgCl$	Et_2AlCl	THF	–85 °C	**8d/9d**	98 : 2	78

[a]All reactions were carried out at a substrate concentration of 0.125 M. [b]Determined by HPLC with UV 254 nm (entries 3, 6, 12) or RI (all others) detection. [c]Isolated yield. [d]Starting material was recovered (44%).

reagents at –85 °C, excellent selectivities of 99:1 and 98:2, respectively, were obtained (entries 11 and 12). These results reveal that lowering reaction temperature in the nucleophilic alkylation of **7** retards, as expected, the Lewis acid-induced C—O bond breaking which produces the hydrazonium ion **C**,[4] thereby causing the predominant S_N2 attack on the initially formed Et_2AlCl–ether complex **B**.

The temperature effect on the Et_2AlCl–mediated formation of the hydrazonium ion is strongly supported by ^1H NMR spectroscopic monitoring of the reaction between the Lewis acid and the hydrazine N,O-acetal **7**: To an NMR tube containing a 0.5 M solution of Et_2AlCl in THF-d_8 was added one-fourth molar quantity of **7** relative to Et_2AlCl via microsyringe at –80 °C. The tube was immediately inserted into the NMR probe maintained at 20 °C and the spectrum was recorded within 2 min (Figure 2, spectrum **b**), during which time the

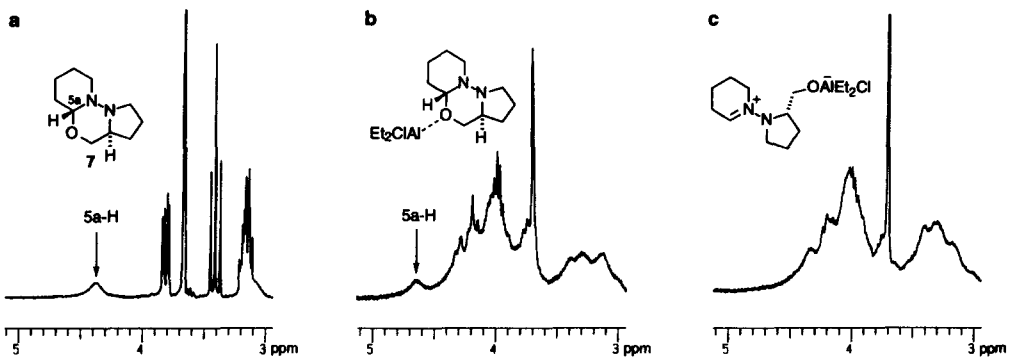
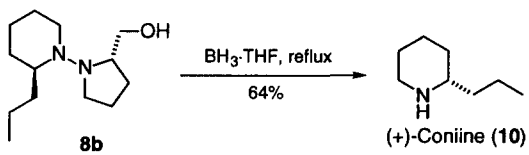


Figure 2. Partial ^1H NMR spectra (THF-d_8) of **7** (**a**) and complexes (**b** and **c**) formed by addition of Et_2AlCl.

temperature of the solution was allowed to rise to –10 °C. After that, the tube was allowed to stand in the probe for 10 min and the spectrum of the sample solution standing at 20 °C was recorded as shown (spectrum **c**). Whereas the free N,O-acetal **7** shows a 5a-H signal at 4.38 ppm (see reference spectrum **a**), inspection of spectrum **b** showed that, upon addition of Et_2AlCl, the 5a-H signal occurs significantly downfield (4.64 ppm) with slight reduction in intensity, indicating that the cyclic hydrazine N,O-acetal structure, wherein the Lewis acid coordinates to the N,O-acetal oxygen (like **B**), is almost alive at –80 °C to –10 °C within 2 min. However, upon standing at 20 °C for 10 min, the 5a-H signal of the Lewis acid–N,O-acetal complex, detected in spectrum **b**, disappeared as shown by spectrum **c**. These results imply that this species is short-lived at an elevated temperature, thus decaying to form the hydrazonium ion. From the above experimental facts and spectroscopic investigations, it is clear that the hydrazine N,O-acetal **7** may react with the Grignard reagents via an S_N2 mechanism with the Lewis acid complex **B** below –80 °C, but at an elevated temperature predominantly via an S_N1 mechanism with the hydrazonium ion **C**.

The developed methodology for diastereomeric alkylation of **7** would be useful in view of its importance in enantioselective preparation of 2-substituted piperidines. We then utilized the inversive isomer **8b**, chromatographically separable as a single diastereomer, for the preparation of (+)-coniine (**10**) that is accepted as one of the standards for the demonstration of chiral methodology.[1d,4a,6] Thus, **8b** was subjected to reductive N—N bond cleavage by treatment with BH_3·THF at reflux. Workup and treatment with aqueous HCl provided the hydrochloride salt of enantiomerically pure (+)-coniine (**10**), mp 219–221 °C (EtOH–ether) (lit.[6e] mp 217 °C); $[\alpha]^{26}_D$ +6.2 (*c* 0.40, EtOH) [lit.[6e] $[\alpha]^{28}_D$ +5.8 (*c* 0.43, EtOH)], in 64% yield.



8b (+)-Coniine (**10**)

In conclusion, we have proved that our methodology involving alkylation of the cyclic hydrazine N,O-acetal with a combination of Et_2AlCl and Grignard reagents reaches a predictable and practical level for the enantioselective preparation of chiral 2-substituted piperidines. Further application to heteroalicycles such as those having the piperidine and pyrrolidine rings, which are of importance from a pharmacological aspect, is under investigation.

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