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A SYNTHESIS OF 2-*EXO*-SUBSTITUTED 2-*ENDO*-AMINONORBORNENES: ORGANOALUMINUM-PROMOTED NUCLEOPHILIC SUBSTITUTION ON 2-*ENDO*-ACETAMIDO-2-*EXO*-METHOXYNORBORNENE

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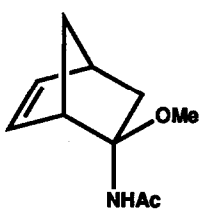
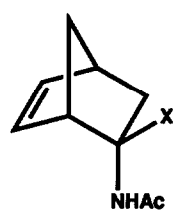
Summary: A variety of 2-*exo*-substituted 2-*endo*-acetamidonorbornenes (**2a-g**) were synthesized in exceedingly high *exo* selectivities by organoaluminum-promoted nucleophilic substitution on 2-*endo*-acetamido-2-*exo*-methoxynorbornene (**1**).

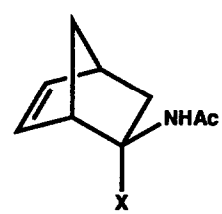
2-*exo*-Substituted 2-*endo*-aminonorbornanes have attracted considerable attention with the discovery of the exciting biological activities.[1,2] The presence of 2-*endo*-amino group is crucial for exhibiting the biological activities.[1,2] In connection with our synthetic studies on search for a new lead compound having intriguing biological activities, we now report a synthesis of 2-*exo*-substituted 2-*endo*-acetamidonorbornenes (**2a-g**) in high *exo* selectivities by organoaluminum-promoted nucleophilic substitution on 2-*endo*-acetamido-2-*exo*-methoxy-norbornene (**1**).



1



2a-g



3a-g

a: X=SCH_2Ph **b:** X=SPh **c:** X=SEt **d:** X= SCH_2CO_2Me
e: X= NHPh **f:** X= C≡C-Ph **g:** X= C≡C-OTHP

The nucleophilic substitutions on *N*-acyl-α-methoxyalkylamines under the influence of acidic catalysts have been well-recognized to proceed through the highly reactive *N*-acyliminium ions and/or *N*-acylimines;[3] the process closely resembles an SN1 reaction. Thus, it would be difficult to obtain **2** selectively by nucleophilic substitution on **1** using an ordinary acidic catalyst.[4] In fact, the reaction of **1**, readily obtained by anodic oxidation[5] of 2-acetamidonorbornene-2-carboxylic acid,[6] with $PhCH_2SH$ in the presence of $SnCl_4$, BF_3OEt_2, Me_3SiOTf, $ZnCl_2$ or HCl gave rise to a mixture of **2a** and **3a** in a ratio of 61:39 , 67:33 , 65:35 , 50:50 or 64:36 , respectively. On the other hand, Nozaki and Oshima noted that in the reaction of allylic phosphates with organoaluminum reagents in a polar solvent, the nucleophilic substitutions presumably take place *via* an intimate ion-pair in a solvent cage, implying the intervention of an SN*i* mechanism.[7] With such information in hand, we examined the reaction of **1** with R_2Al-X (**4a-g**) type organoaluminum reagents .

Treatment of **1** with Me_2Al-SCH_2Ph (**4a**)[7] in CH_2Cl_2 for 1 hr at room temperature gave a mixture of **2a** and **3a** in a ratio of 99 : 1 (run 1).[8] A similar *exo* selectivity was also observed in the reaction using THF as

solvent. It is noteworthy that the use of hexane[7] lowered the *exo* selectivity, the **2a/3a** ratio being 81 : 19. In marked contrast with the above results, the addition of $AlMe_3$ to a mixture of **1** and $PhCH_2SH$ in CH_2Cl_2 resulted in **2a/3a** ratio of 68 : 32. The results suggest that R_2Al-X type organoaluminum reagents would make the nucleophilic substitution proceed apparently *via* an S*Ni* mechanism. The generality of the present nucleophilic substitution is indicated in Table 1. Organoaluminum reagents having other sulfur (runs 2-4) and nitrogen (run 5) functionalities as nucleophilic parts also worked effectively. Furthermore, it should be noted that carbon-carbon bond forming reactions were realized by this operation (runs 6,7). The structures of all products reported herein were unambiguously determined by X-ray crystallographic and/or NMR analyses.[9]

Table 1. Organoaluminum-promoted nucleophilic substitution [1]

	R_2Al-X (4)			
run	R	X	Yield (%)[2]	ratio (**2**/**3**) [3]
1	Me	a	81	99 : 1
2	Me	b	84	99 : 1
3	Me	c	81	97 : 3
4	Me	d	59	98 : 2
5	Me	e	33	97 : 3
6	Et	f	70	98 : 2
7	Et	g	72	97 : 3

1) The reaction was carried out on a 10 mmol scale in CH_2Cl_2 at room temperature.
2) Isolated yield of a mixture of **2** and **3** by silica gel column chromatography.
3) The ratio was determined by HPLC of the reaction mixture.

This method should find application in the synthesis of 2-*exo*-substituted 2-*endo*-aminonorbornanes[10] having interesting biological activities.[11]

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References and Notes

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4. Seebach *et al.* reported the Lewis acid catalyzed nucleophilic substitutions on *N*-acyl-α-methoxyalkylamines. However, high diastereoselectivities were not observed. See, Seebach, D. ; Charczuk, R. ; Gerber, C. ; Renaud, P. *Helv. Chim. Acta.*, **1989**, *72*, 401, and references cited therein.
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8. The reaction of 2-*endo*-acetamido-2-*exo*-methoxynorbornane with **4a** was also carried out under the same conditions to give almost the same *exo* selectivity.
9. The shielding effect of the 5,6-double bond of **2** shifts the NMR signals of the methyl protons of the acetamido group of **2** to a higher field than those of **3**. See, ref. 6.
10. We have not examined this type of reaction using 2-*exo*-acetamido-2-*endo*-methoxynorbornene because of the difficulty in the preparation of the above methoxylated compound by chemical or electrochemical methods.
11. Some of these compounds reported herein showed moderate antiulcer activities. The details will be reported elsewhere in near future.

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