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Stereoselective C4 alkylation of NAD(P)$^+$ analogs

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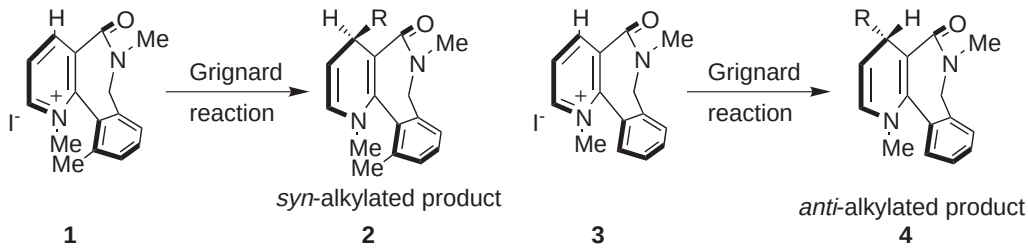
Abstract—Alkylation of NAD(P)$^+$ analogs with Grignard reagents gave C4-alkylated NAD(P)H analogs in high regio- and stereoselectivity.

Alkylation of **1** and **3** with Grignard reagents gave C4-alkylated products **2** and **4** respectively, in high regio- and stereoselectivity (Scheme 1).

NAD(P)$^+$ analog **1** has a steric hindrance between two proximate methyl groups, which prevents a phenylene group from a flip and, therefore, makes the orientation of a carbonyl group stable at room temperature; two enantiomers of the analog are separable.[1] The corresponding NAD(P)H analog **2** (R=H) also has a stable configuration; dithionite reduction of **1** in D_2O affords **2** (R=D) which is deuterated preferentially in *syn* position with respect to the orientation of the carbonyl group and also in which a flip does not occur.[1] On the other hand, flip, i.e. racemization is observed in NAD(P)$^+$ analog **3** which has no methyl group in an phenylene group, and dithionite reduction of **3** in D_2O shows no stereoselectivity.[2]



Scheme 1.

Table 1. Alkylation of **1**and **3** with Grignard reagents

Model	RMgX	Yield (%)[a]	C4-Alkylated				C2-Alkylated[b]
			syn Side	:	*anti* Side	:	
1	MeMgI	67	98	:	2	:	0
1	EtMgI	75	98	:	2	:	0
1	*i*PrMgBr	72	97	:	3	:	0
3	MeMgI	60	<2	:	>98	:	0
3	*i*PrMgBr	62	<2	:	>98	:	0

[a] Total isolated yield of C4-alkylated products.
[b] Determined based on ^{1}H NMR spectra of the crude products.

Keywords: NAD(P)(H) analog; Grignard reaction; stereoselection; regioselection.
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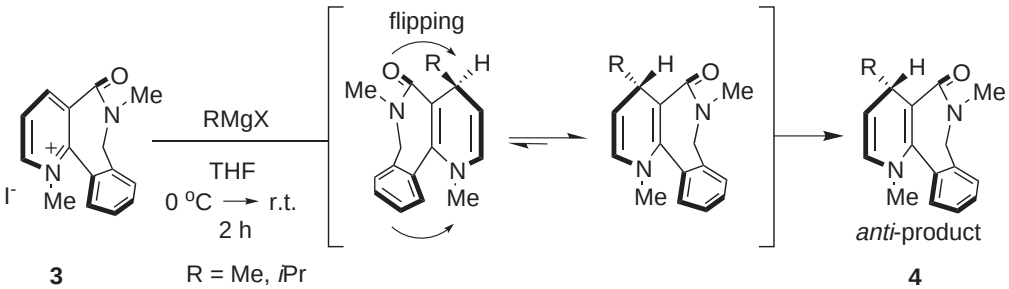
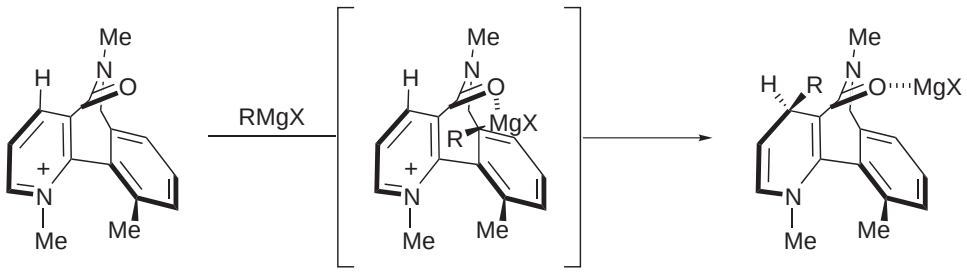


Scheme 2.



Scheme 3.

The *syn* selectivity in the reduction of **1** is so interesting, that we studied reductive alkylation of **1** and **3** with Grignard reagents (Scheme 1).

Racemic analogs **1** and **3** were treated in tetrahydrofuran with Grignard reagents under usual conditions.[3] Relative configuration between the carbonyl and C4-alkyl group of the products were assigned on the basis of configuration of 1,4-dihydropyridine form **2** (R=H) previously reported; a chemical shift of C4-*syn*-H in ^{1}H NMR spectrum of **2** (R=H) appears in more downfield than that of C4-*anti*-H due to anisotropic effect of the carbonyl group.[1] These results are summarized in Table 1.[4]

No C2-alkylated product[5–9] is detected by ^{1}H NMR spectroscopy in all cases. C4-*syn*-alkylated **2** is almost the sole product in the case of **1**. C4-*anti*-alkylated product, which is prepared by the oxidation of **2** and the following reduction according to the previous reported manner,[1] makes up a small component. This *syn* selectivity of the alkylation is higher than that of the dithionite reduction that affords the *syn* and *anti* products in 80:20.[1]

On the contrary, *anti*-alkylated **4** (R = Me, *i*Pr) is exclusively obtained in the case of **3**. This stereochemical difference would be explained in Scheme 2: the Grignard reagent attacks kinetically in the *syn* side of C4 position of **3**, then the carbonyl group inverts its configuration to avoid large steric hindrance between the carbonyl and the alkyl group, resultantly, affording thermodynamically stable *anti*-alkylated **4**. Unfortunately, the inversion was not observed. Probably, it would be so fast that we could not isolate the *syn*-alkylated product. On the other hand, **2**, the *syn*-alkylated product from **1**, would be formed kinetically, and then not subjected to inversion because of the steric hindrance described above.

The *syn* selectivity of the alkylation would result from that the carbonyl oxygen of the analog coordinates to magnesium nucleus in the Grignard reagent (Scheme 3). Since the carbonyl oxygen exists in one side of the pyridinium face, the coordination places the Grignard reagent in the same side in the reaction. Thus, the Grignard reagent is forced to attack **1** in the *syn* side, even if this side is sterically more crowded than the other. The stereo-determining coordination would also be concerned in the oxidation of reduced form **2** (R=H) with *p*-benzoquinone derivatives in the presence of Mg^{2+}.[10,11] These results show that the stereochemistry is controlled by the electrostatic effect only.

It has been proposed that stereochemistry of reactions of NAD(P)$^+$/NAD(P)H is influenced by the orientation of a carbonyl dipole.[12] The series of studies with NAD(P)$^+$/NAD(P)H analogs **1**/**2** and **3**/**4** signifies the role of the carbonyl orientation, as well as suggesting that the stereochemistries are controlled by electrostatic acceleration and not by steric decelaration of the reactions.

Further studies on this series are in progress and will be reported in due course.

References

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8133. Half-life for racemization of **3** ((+)-camphorsulfonate salt) in CH_3CN is 13.6 min. at 25.0°C.

3. In a typical procedure, a solution of Grignard reagent (2 equiv.) in ether was added to a stirred and cooled suspension of **1** (**3**) in dry tetrahydrofuran and the mixture was stirred for 2 h at room temperature followed by hydrolysis with an aqueous 30% NaOH solution. After standard work-up, a crude product was purified by column chromatography on alumina.
4. Fully satisfactory ^{1}H NMR spectrometry data were obtained for all alkylated compounds. Selected ^{1}H NMR (δ ppm ($CDCl_3$)) data for *syn*-isopropyl-**2**: δ 0.89 (d, 3H, *i*Pr(CH_3), $J = 7.0$ Hz), 0.97 (d, 3H, *i*Pr(CH_3), $J = 7.0$ Hz), 2.35 (s, 3H, Ph-CH_3), 2.52 (dq, 1H, *i*Pr(CH), $J = 4.0$ Hz, $J = 7.0$ Hz), 2.66 (s, 3H, N1-CH_3), 2.94 (s, 3H, N6-CH_3), 3.18 (dd, 1H, C4-H_{anti}, $J_{3,4anti} = 5.7$ Hz, $J = 4.0$ Hz), 3.74 (d, 1H, CH_2, $J = 13.8$ Hz), 4.62 (d, 1H, CH_2, $J = 13.8$ Hz), 4.77 (dd, 1H, C3-H, $J_{2,3} = 7.8$ Hz, $J_{3,4anti} = 5.7$ Hz), 6.05 (d, 1H, C2-H, $J_{2,3} = 7.8$ Hz), 7.04–7.23 (m, 3H, arom.). *anti*-Isopropyl-**2**: δ 0.93 (d, 3H, *i*Pr(CH3), $J = 7.0$ Hz), 0.97 (d, 3H, *i*Pr(CH3), $J = 7.0$ Hz), 1.62 (dq, 1H, *i*Pr(CH), $J = 4.0$ Hz, $J = 7.0$ Hz), 2.25 (s, 3H, Ph-CH_3), 2.58 (s, 3H, N1-CH_3), 2.92 (s, 3H, N6-CH_3), 3.76 (d, 1H, CH_2, $J = 14.1$ Hz), 3.88 (dd, 1H, C4-H_{syn}, $J_{3,4syn} = 5.2$ Hz, $J = 4.0$ Hz), 4.75 (d, 1H, CH_2, $J = 14.1$ Hz), 4.75 (dd, 1H, C3-H, $J_{2,3} = 7.3$ Hz, $J_{3,4syn} = 5.2$ Hz), 5.96 (d, 1H, C2-H, $J_{2,3} = 7.3$ Hz), 7.05–7.23 (m, 3H, arom.). *anti*-Isopropyl-**4**: δ 0.93 (d, 3H, *i*Pr(CH3), $J = 6.8$ Hz), 0.94 (d, 3H, *i*Pr(CH3), $J = 6.8$ Hz), 1.54 (dq, 1H, *i*Pr(CH), $J = 4.2$ Hz, $J = 6.8$ Hz), 2.75 (s, 3H, N1-CH_3), 2.98 (s, 3H, N6-CH_3), 3.83 (d, 1H, CH_2, $J = 14.0$ Hz), 3.89 (dd, 1H, C4-H_{syn}, $J_{3,4syn} = 5.5$ Hz, $J = 4.2$ Hz), 4.69 (d, 1H, CH_2, $J = 14.0$ Hz), 4.83 (dd, 1H, C3-H, $J_{2,3} = 7.2$ Hz, $J_{3,4syn} = 5.5$ Hz), 6.04 (d, 1H, C2-H, $J_{2,3} = 7.2$ Hz), 7.25–7.37 (m, 4H, arom.).
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