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Regiocontrol in Alkylations of α-Silyl Hydrazones

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Abstract

The regioselectivity of alkylation of α-silyl hydrazones can be controlled by the appropriate choice of base, reaction temperature and solvent, and hydrazone moiety to afford either kinetic or thermodynamic products.

Keywords: alkylation; hydrazones; regiocontrol; silicon compounds

Recent reports [1,2] have described the preparation and synthetic utility of α-silyl hydrazones. In the course of our research we required the hydrazones **3c** and **3d** with an α-silyl group on one side and a β-tertiary carbinol centre on the other. In general, a hydrazone will deprotonate regioselectively on the less substituted side, forming an $E_{CC}Z_{CN}$ azaallylanion [3,4] which can then be alkylated. We thus proposed to synthesize these compounds via sequential silylation and aldol reactions of the corresponding metallated acetone hydrazones. Aldol reactions of the silylated achiral dimethylhydrazone **1a** with 2-hexanone under standard deprotonation and alkylation conditions (LDA; -78°C to 0°C for deprotonation, -78°C for alkylation) proceeded in reasonable yield (50-60%) with the desired regioselectivity to give the alcohol **3c** (Scheme 1), but the corresponding chiral (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP) [4-6] hydrazone **1b** gave very low yields of alcohol **3d**, even when the ketone was added at 0°C. In contrast, alkylation of the RAMP hydrazone **1b** under similar conditions with methyl iodide occurred adjacent to the silyl group to form exclusively the product **2b**. Enders and co-workers [1] observed similar regioselectivity in alkylations of α-silyl (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazones, and alluded to the apparent influence of the base in this regard. No details were given, however, other than the statement that in a few cases *n*-BuLi was crucial for this regioselective deprotonation adjacent to the silyl group. Accordingly we have

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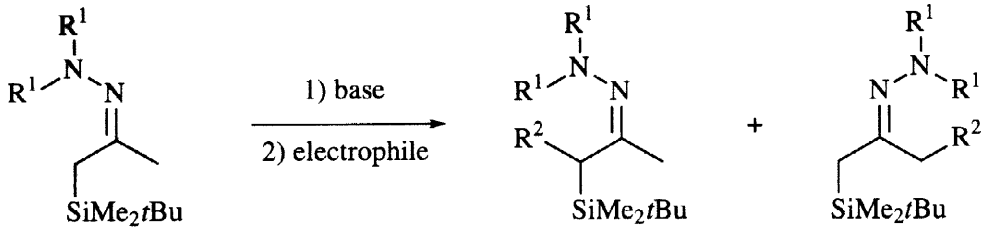
examined further the ionisation and subsequent alkylation of the dimethyl and RAMP hydrazones **1a** and **1b** under a variety of conditions.[1]



1a R^1 = Me
1b NNR^1_2 = RAMP

2a $R^1 = R^2$ = Me
2b NNR^1_2 = RAMP; R^2 = Me

3a $R^1 = R^2$ = Me
3b NNR^1_2 = RAMP; R^2 = Me
3c R^1 = Me; R^2 = C(OH)(Me)*n*Bu
3d NNR^1_2 = RAMP; R^2 = C(OH)(Me)*n*Bu

Scheme 1. Alkylation of α-Silyl Hydrazones

Methylation of the silylated achiral dimethylhydrazone **1a** after deprotonation with LDA under the standard conditions in THF at -78 to 0°C was efficient, but equally divided between the two possible alkylation sites (Table 1, entry 1). Similar ratios of the isomers **2a** and **3a** were obtained after ionisation over the same temperature range with *t*-BuLi or *n*-BuLi in THF (entries 3 and 5). The primary alkylated regioisomer **3a** could, however, be obtained preferentially by deprotonation with the bulkier bases LDA or *t*-BuLi in THF at -78°C, provided that the anion was maintained and alkylated at this temperature (entries 2 and 4). Deprotonation with *n*-BuLi even at -78°C was not regioselective (entry 6). THF proved to be a superior solvent to ether for alkylation at the less hindered site, ionisation with LDA in the latter solvent being less regioselective even at -100°C (entries 7, 8 and 2).

In contrast, methylation of the silylated RAMP hydrazone **1b** after deprotonation with either LDA, *t*-BuLi or *n*-BuLi under the standard conditions in THF at -78°C to 0°C, gave virtually exclusively the secondary alkylation product **2b** (Table 2, entries 1, 3 and 5). The primary methylation product **3b** could again be obtained preferentially following deprotonation with LDA or *t*-BuLi, but not *n*-BuLi, by maintaining the entire process at -78°C (entries 2, 4, and 6).

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[1]Procedure for hydrazone alkylation: Hydrazone **1** (0.20 mmol) was added to a solution of LDA (1.2 eq) in THF or ether (1.0 mL) at -78°C. When *n*-BuLi or *t*-BuLi was used, the base was added to the hydrazone in THF or ether. After 5 min, the solution was warmed to 0°C, stirred for 1hr, then cooled to -78°C, at which point iodomethane or 2-hexanone (0.40 mmol, 2.0 eq) was added. Alternatively, the ionisation was carried out for the same time at -78°C. The reaction was allowed to warm to rt overnight, then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under vacuum. The crude product containing (*Z*)-2 and (*E*)-3 was analysed by ^1H NMR spectroscopy, from which the ratio **2**:**3** was determined. The regioisomers could be partially resolved by flash column chromatography (silica gel 5 g, pentane:ether 10:1), which was accompanied by hydrazone isomerisation, to give fractions containing predominantly the (*E*) and (*Z*) isomers of **2** and **3** respectively, in isolated yields corresponding to those observed in the crude product.

Table 1

Alkylation of the dimethylhydrazone 1a with iodomethane

entry	base	solvent	temperature of anion formation (°C)	temperature of alkylation (°C)	ratio[a] **2a:3a**	yield (%)[a] **2a + 3a**
1	LDA	THF	-78 to 0	-78	52:48	80
2	LDA	THF	-78	-78	5:95	64
3	*t*-BuLi	THF	-78 to 0	-78	58:42	80
4	*t*-BuLi	THF	-78	-78	20:80	100
5	*n*-BuLi	THF	-78 to 0	-78	50:50	100
6	*n*-BuLi	THF	-78	-78	45:55	92
7	LDA	Et_2O	-78	-78	36:64	72
8	LDA	Et_2O	-100	-100	30:70	90

a) Determined by integration in ^1H NMR spectra of crude products.

Table 2

Alkylation of the RAMP hydrazone **1b** with iodomethane

entry	base	solvent	temperature of anion formation (°C)	temperature of alkylation (°C)	ratio[a] **2b:3b**	yield (%)[a] **2b + 3b**
1	LDA	THF	-78 to 0	-78	100:0	70
2	LDA	THF	-78	-78	28:72	95
3	*t*-BuLi	THF	-78 to 0	-78	>90:<10	70
4	*t*-BuLi	THF	-78	-78	30:70	95
5	*n*-BuLi	THF	-78 to 0	-78	100:0	46
6	*n*-BuLi	THF	-78	-78	75:25	95

a) Determined by integration in ^1H NMR spectra of crude products.

The present results, and the observation of Enders and co-workers [1], can be rationalized as follows. When the entire reaction is conducted at -78°C, the bulkier bases LDA and *t*-BuLi deprotonate predominantly the less hindered side of the hydrazones **1a** and **1b**, affording kinetically-derived anions which yield the primary alkylation products **3a** and **3b**. This kinetic regioselectivity is highest for deprotonation of the dimethylhydrazone by LDA, and decreases somewhat with the use of the RAMP hydrazone or *t*-BuLi. Deprotonation with the less bulky *n*-BuLi is completely non-regioselective for the dimethylhydrazone **1a**, and favours the secondary site for the RAMP hydrazone **1b**. The better kinetic regioselectivity observed in THF compared to ether may be due to solvent aggregates forming around the base. Warming the metallated hydrazones to 0°C allows thermodynamic equilibration of the kinetic anions with the more substituted silyl-stabilized hydrazone anions, which subsequently afford the secondary alkylation products **2a** and **2b**. The position of the thermodynamic equilibrium is markedly affected by the structure of the hydrazone moiety itself. In the case of the dimethylhydrazone **1a** there is little energy

difference between the primary and secondary azaallylanions, whereas under thermodynamic conditions the RAMP hydrazone affords the secondary anion and its alkylation product almost exclusively. The regioselectivity of the α-silyl hydrazone alkylation can thus be controlled by the appropriate choice of base, reaction temperature and solvent, and hydrazone moiety. An alternative approach to the alkylated α-silyl hydrazones **3a-d** which will not, however, be available in more complex cases, involves reversing the order in which the substituents are introduced. Silylation of the alkylated hydrazone obeys the normal rules[3,4] and proceeds on the less substituted carbon.

The low yields of the alcohol **3d** initially encountered in the aldol reaction of the RAMP hydrazone **1b** (Table 3, entries 1-3) can now be explained by equilibration of the primary anion under thermodynamic conditions to a secondary anion, which is too hindered to react with 2-hexanone. Indeed, by employing reaction conditions optimized for generation of the kinetic anion substantial yields of aldol product **3d** could be obtained (entry 4).

Table 3

Aldol reaction of the RAMP hydrazone **1b** with 2-hexanone

entry	base	solvent	temperature of anion formation (°C)	temperature of alkylation (°C)	diastereo-selectivity[a] (% de)	yield (%)[a] **3d**
1	LDA	THF	-78 to 0	-78	n.d.[b]	0
2	LDA	THF	-78 to 0	0	n.d.	22
3	*n*-BuLi	THF	-78 to 0	-78	n.d.	<10%
4	*t*-BuLi	THF	-78	-78	26	64

a) Determined by integration in ^{1}H NMR spectra of crude products.

b) Not determined.

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