BECKMANN REARRANGEMENT OF OXIME SULFONATES BY GRIGNARD REAGENTS

Kazunobu Hattori, Keiji Maruoka, and Hisashi Yamamoto Department of Applied Chemistry, Nagoya University Chikusa, Nagoya 464, Japan

Summary The Beckmann rearrangement of oxime sulfonates by Grignard reagents provides an efficient and general entry to α -alkyl- and α , α -dialkylamines in good yields

Recently we disclosed a new synthetic procedure for α -alkylation of amines in which alkylaluminum compounds were employed as amphoteric reagents to induce the Beckmann rearrangement of oxime sulfonates as well as alkylate the intermediary iminocarbonium ions ^{1,2} Despite the generally superior results obtained in the reaction of organoaluminum reagents, we have sought to extend the investigation to other organometallics with the object of finding the ultimate with regard to efficiency and flexibility of this transformation. A survey was therefore made of a variety of organometallics which would have the latent possibilities of a similar function to organoaluminum reagents. Although most of these were either totally ineffective (RLi) or less satisfactory (RZnX) as reagents, an extraordinarily interesting and promising result was obtained with <u>simple Grignard reagents in nonpolar solvents</u> ³ Thus, treatment of oxime sulfonates with Grignard reagents furnished the immes which were converted to α -alkylamines with disobutylaluminum hydride (DIBAH), or further alkylated using allylic or propargylic Grignard reagents⁴ to give α , α -dialkylamines (eq 1). ⁵



A typical experimental procedure for α -alkylation of amines by Grignard reagents follows (entry 2) <u>n</u>-Butylmagnesium bromide (0 5 mL of a 3 <u>M</u> ethereal solution, 1 5 mmol) was added to a solution of cyclohexanone oxime methanesulfonate (185 mg, 1 mmol) in dry toluene (5 mL) at -78°C, and the resulting mixture was stirred at -78°C for 5 min and at 0°C for 1 h. DIBAH (2 mL of a 1 <u>M</u> n-hexane solution, 2 mmol) was added at 0°C and the mixture was stirred at 25°C for 1 h. Then this was poured onto a 5% NaOH solution (40 mL), shaked well, and centrifuged to remove the white gel. Extractive work-up with dichloromethane followed by column chromatography on silica gel (<u>1</u>-PrNH₂-ether-<u>n</u>-hexane as eluant) furnished the desired 2-<u>n</u>-butylazacycloheptane (98 mg, 63% yield) as a colorless oil.

As listed in Table I, this method has a wide utility for a large range of oximes and Grignard reagents

Entry	Oxime Sulfonate	RMgX (equiv) ^a	Conditions ^b (°C, h)	R'MgX (equiv) c, d	Product ^e	Yield (%)
1 c	H ₃ (CH ₂)7 N _M OMs	CH ₃ MgI (4)	0, 1 25, 1	сн ₃ (CH ₂ ² , H CH ₃	36
2	\frown	BuMgBr (1 5)	0, 1			63
3	\mathbf{Y}	CH ₃ MgI (1 5)	0, 1	$CH_2 = CHCH_2 MgBr (2)^{\frac{h}{2}}$		72
4	N_OMs	CH ₃ MgI (1 5)	0, 1	HC≡CCH ₂ MgBr (4)	HR	66
5	\sim	CH ₃ MgI (1 5)	0, 1		\sim	66 (42) <u>ⁱ</u>
6	ς	BuMgI (1 5)	0, 1		\mathcal{L}	63
7	\bigvee	BuMgBr (1 5)	0, 1		N R'	67
8	N OMs	BuMgCl (1.5) ^{<u>f</u>}	0, 1		H \ R	40
9		OctylMgBr (1.5)	0, 1			68
10		CH ₂ MgI (1.5)	0, 1	CH ₂ =CHCH ₂ MgBr (2) ^{<u>h</u>}		76
11		CH ₃ MgI (1.5)	0, 1	HC≡CCH ₂ MgBr (4)		79
12		CH ₃ MgI (1.5)	-78, 1		~	52
13		BuMgBr (4)	-78, 1			55
14	Ň OMs	BuC≡CMgBr (3) ^g	0, 1		H	47

Table I. Synthesis of α -Alkyl- and α , α -Dialkylamines

a) The Grignard reagent was prepared from an alkyl halide and metallic magnesium in ether. b) Rearrangement was carried out initially at -78°C, and then under the conditions indicated. c) Unless otherwise stated, the resulting ketimine was reduced with DIBAH (4 equiv) at 25°C for 1 h. d) The second alkylation was performed at 0°C for 1~3 h. e) R' = H in case of DIBAH reduction f) Bryce-Smith, D, Blues, E T <u>Org</u> <u>Syn Coll Vol V</u>, 1973, 1141 g) Prepared from 1-hexyne and BuMgBr in ether. h) Grummitt, O, Budewitz, E P, Chudd, C C <u>Org Syn Coll. Vol IV</u>, 1963, 748 i) The yield in a parenthesis refers to the result obtained in dichloromethane-ether solvent

The use of ether-duchloromethane as solvent under the similar reaction conditions produced the desired amines in lower yields (entry 5) In pure ether or tetrahydrofuran, no or very little α -alkylation products were produced An alkylmagnesium chloride is less effective compared to the corresponding alkylmagnesium bromide or iodide (entry 6~8) Notably, the propargyl group can be introduced in a regiospecific manner (entry 4, 11) providing an important precursor for the synthesis of various naturally occurring γ -ketoamines^{6,7}

REFERENCES AND NOTES

- 1. Hattori, K., Matsumura, Y., Miyazaki, T., Maruoka, K., Yamamoto, H J. Am. Chem. Soc., 1981, 103, 7368.
- 2. Matsumura, Y, Maruoka, K., Yamamoto, H. Tetrahedron Lett., in press
- 3 Aromatic hydrocarbons (benzene or toluene) are preferable as solvent.
- 4. The propargylic lithium reagents (e.g. $Me_3SiC \equiv CCH_2Li$) can be used as well.
- 5. All new compounds have been characterized spectrometrically and analytically.
- 6. For example, piperidine alkaloids such as Anaferine, Anahygrine, and Norlobelamine possess γ -ketoamino structures
- 7. This work was generously supported by the Naito Science Foundation.