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## Enantioselective Synthesis of Nitrogen Derivatives by Allyl Grignard Addition on Optically Active Nitroalkanes

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Reaction of optically active nitroalkanes with allyl Grignard reagents affords *E–Z* mixtures of nitrones which can be reduced to chiral hydroxylamines and amines.

Nitrogen containing molecules having optical activity occupy a dominant position in the field of biologically active substances.<sup>1</sup> This provides a great incentive for developing new methods to control the stereochemical outcome of chemical transformations involving this class of compounds. Recently we have reported a very efficient synthesis of nitrones starting from aromatic and aliphatic nitrocompounds and 2-butenyl-magnesium chloride  $1^2$  (Scheme 1).

Interestingly when simple nitroalkanes are used as substrates in this reaction, the non-conjugate nitrone **4** is preferentially formed over the apparently more stable regioisomer.<sup>3</sup> Since nitrones represent a versatile class of compounds in organic synthesis<sup>4</sup> we decided to check the degree of enantioselection for our reaction using as substrate some nitroalkanes bearing a chiral centre in the proximity of the nitro-group. For this we chose (S)-(2-benzyloxy)-1-nitropropane **5** easily obtained from the corresponding iodide<sup>5</sup> by nucleophilic displacement with nitrite anion in dimethyl sulphoxide.<sup>†</sup>

Reaction of 5 with 1 in tetrahydrofuran (THF) at -70 °C gave the nitrones 6 in 86% yield as equimolar mixture of E-Z



Scheme 1 Reagents and conditions: i, THF, -70 °C, ii, MeCO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, -70 °C to room temp.

stereoisomers, as well as the conjugated isomer 7 in 10% yield. Product **6** is easily separable from 7 by column chromatography and its reduction with NaBH<sub>4</sub> in MeOH afforded hydroxylamine **8** in 92% yield with the new chiral centre of *R* configuration‡ (Scheme 2). No detectable amount of the *S* isomer has been found in this reaction.



Scheme 2 Reagents and conditions: i and ii as for Scheme 1; iii, NaBH<sub>4</sub>, MeOH, 0 °C, 92%; iv, HCl (0.5 mol dm<sup>-3</sup>), CHCl<sub>3</sub>, 12 h, room temp.; v, LiAlH<sub>4</sub>, THF, 0 °C

<sup>‡</sup> A typical experimental procedure is as follows: **5** (0.02 mol, 3.9 g) is dissolved in dry THF (50 ml) and cooled to -70 °C. Grignard reagent **1** (0.22 mol) is then added dropwise and after 20 min the reaction mixture is quenched by addition of acetic acid (0.03 mol, 1.75 ml) in CH<sub>2</sub>Cl<sub>2</sub> (25 ml) at -70 °C. The temperature is allowed to rise to room temp. and usual work-up gives the crude product which is purified by column chromatography (hexane–ethyl acetate–ethanol 6:3:1), 3.96 g, 86% yield). The mixture of nitrones **6** dissolved in MeOH (50 ml), is cooled at 0 °C, NaBH<sub>4</sub> (0.0186 mol, 0.7 g) is then added and stirring continued at this temperature for 25 min. Usual work-up affords crude compound **8** which can be purified by column chromatography (hexane–ethyl acetate 7:3) (3.67 g, 92% yield).

Spectroscopic data for 8: m.p. 63 °C,  $[\alpha]^{20}$ <sub>D</sub> + 5.61° (*c* 4.65, EtOH); IR v<sub>max</sub>/cm<sup>-1</sup>, 3400 (OH); <sup>1</sup>H NMR (300 MHz)  $\delta$  1.20 (d, 3H, *J* 6.5 Hz), 1.25 (d, 3H, *J* 6.8 Hz), 2.80 (d, 2H, *J* 6.5 Hz) 3.20–3.35 (m, 1H), 3.80–3.90 (m, 1H), 4.50–4.65 (m, 2H), 5.10–5.20 (m, 2H), 5.45 (bs, 1H), 5.80–5.95 (m, 1H) and 7.20–7.40 (m, 5H).

<sup>&</sup>lt;sup>†</sup> Selected spectroscopic data for **5**: m.p. 51 °C;  $[\alpha]^{20}_{D}$  +11.9° (c 2.03, EtOH); <sup>1</sup>H NMR (300 MHz)  $\delta$  1.30 (d, 3H, *J* 6.0 Hz), 4.25–4.35 (m, 1H), 4.38 (d, 1H, *J* 3.8 Hz), 4.51 (d, 1H, *J* 3.8 Hz), 4.70 (d, 1H, *J* 11.3 Hz), 4.80 (d, 1H, *J* 11.3 Hz) and 7.22–7.45 (m, 5H).

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Scheme 3 Reagents and conditions: as for Scheme 2



Fig. 1 Transition state for formation of 6

The absolute stereochemistry has been assigned by hydrolysis of the nitrones to the parent hydroxylamine which upon reduction with LiAlH<sub>4</sub> afforded amine 9 of known configuration. {N-2,4-Dinitrophenyl derivative  $[\alpha]^{22}$ <sub>D</sub> -145.6° (c 1, EtOH); Lit.<sup>6</sup> [ $\alpha$ ]<sup>22</sup><sub>D</sub> –146° (*c* 1, EtOH)}. Lower enantioselectivity is obtained if the chiral centre is shifted one carbon atom away from the nitro-group. Nitroalkane 107 gave a mixture of nitrones which after reduction produced two diastereoisomeric hydrolyamines 11 and 12 in a 6:4 ratio.

Some allyl Grignard reagents other than 1 have been used for this reaction and the relative amount of hydroxylamines obtained after reduction of the corresponding nitrone derivative are reported in Scheme 3.

The all-equatorial substituents conformation for the proposed transition state chelation model (Fig. 1) seems to be the most probable pathway for our reaction.8 Since allylmagnesium reagents undergo fast E-Z isomerisation<sup>9</sup> the most plausible assumption is that only one of the two possible configuration reacts preferentially with the nitro-group with consequent formation of a single stereoisomer. We are currently looking for some experimental data to confirm this suggestive hypothesis. No selectivity in the subsequent formation of the nitrone from the intermediate 2 has been shown.

It is also evident that any change of the six member ring geometry of the transition state as occurs with compound 10 will result in a decrease of the enantioselectivity of the reaction. A similar effect could be caused by an increase of the steric hindrance of the Grignard reagent as in 13 and 14. Mechanistic studies and synthetic developments of these reactions are currently in progress in our laboratory.

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