

0040-4039(95)02039-X

One-pot Synthesis of 2-Alkyltetrahydropyran-3-ones from 3-Nitro-5,6-Dihydro-4H-Pyran and Grignard Reagents

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Abstract: 3-Nitro-5,6-dihydro-4H-pyran reacts with primary aliphatic and benzylic Grignard reagents and, in suitable hydrolysis conditions, gives the corresponding 2-alkyltetrahydropyran-3-ones in satisfactory yields.

We recently reported that the 1,4 conjugate addition of organoalanes to 3-nitro-5,6-dihydro-4H-pyran (1) followed by hydrolytic work-up of the resulting aluminum nitronates affords aldehydes.¹ Interestingly, it was found that only the reaction of 1 with triisobutylaluminum gives either 3-methylbutanal (70 % yield) or 2-*i*.butyltetrahydropyran-3-one (56 % yield), depending on the hydrolysis conditions (3 M and 0.8 M HCl, respectively).¹

Owing to the utility of 2-alkyltetrahydropyran-3-ones in organic synthesis,² it seemed logical to investigate the applicability of our methodology to the synthesis of such compounds. In this context, the choice of Grignard reagents rather than organoalanes, as nucleophiles in the Michael-type reaction with 1, was dictated by both the self-immolative nature of organoalanes and the easier preparation and manipulation of Grignard reagents as well as our interest in exploring the reactivity of 1 towards other unstabilized carbanions.

The results of this study are summarized in the Table. As shown, the reaction of primary alkyl Grignard reagents with 1 provided intermediate magnesium nitronates which, upon suitable hydrolysis, were converted into the corresponding 2-alkyltetrahydropyran-3-ones (2 a-c, g).

Mild hydrolysis conditions (0.2 M HCl) could be used for the preparation of 2-*i*.butyltetrahydropyran-3one (**2 a**) and 2-*n*.butyltetrahydropyran-3-one (**2 b**). The Nef reaction did not occurr when the same procedure was applied to magnesium 2-*n*.eptyl- and 2-benzyltetrahydropyran-3-nitronates: only 2-*n*.eptyl- and 2-benzyl-3nitrotetrahydropyrans were isolated, respectively. However, the use of a mixture of 0.2 M HCl / THF (4/1 v/v) followed by usual work-up and purification gave the desired 2-*n*.eptyl- and 2-benzyltetrahydropyran-3-ones (**2 c** and **2 g**, respectively) in excellent yields. It is noteworthy that, in good agreement with previous observations,¹ the more lipophilic nature of the transferred alkyl chain requires the use of a water-soluble ethereal cosolvent in order for the Nef reaction to take place.

Unfortunately, when secondary alkylic and arylic Grignard reagents were employed, it was not possible to identify suitable hydrolysis conditions to improve the yield in the corresponding tetrahydropyran-3-ones (2 **d-f**), since such compounds were always contaminated by the corresponding aldehydes and nitroderivatives (Table). Neither 2 h nor ept-2-ynal were found when magnesium 2-(hex-1'-ynyl)-tetrahydropyran-3-nitronate was hydrolyzed in experimental conditions suitable to promove the solvolytic Nef reaction (Table).

To summarize, the paper deals with the reactivity of 1 towards Grignard reagents and increases the knowledge about the behaviour of α -nitroalkenes towards such organometallics.³ The overall findings indicate that: i) 3-nitro-5,6-dihydro-4H-pyran (1) well tolerates Grignard reagents; ii) these organometallics are suitable to perform the regioselective conjugated alkylation of 1; iii) as far as the investigated cases are concerned, it is possible to convert the magnesium nitronates arising from the addition of primary aliphatic and benzylic Grignard reagents to 1 into the corresponding 2-alkyltetrahydropyran-3-ones (2) in high yields; iv) the yields in

2 drop when secondary and phenyl groups are transferred and v) the solvolytic Nef reaction fails in the case of magnesium 2-(hex-1'-ynyl)-tetrahydropyran-3-nitronate (Table).

Table: Synthesis of 2-Alkyltetrahydropyran-3-ones from 1 and Grignard Reagents^{a,b}



a) All reactions were performed at least twice and, if not otherwise stated, THF was used as solvent; b) Spectral data (IR, NMR, Mass) confirmed the structure of the recovered compounds; c) See Experimental; d) Glc evaluation; minor amounts of unknown products were rejected; numbers in brackets are isolated yields of pure compounds; e) Reaction performed in Et₂O; f) GC-MS analysis; g) Minor amounts of the corresponding aldehyde were also detected; the same compound became the main reaction product when the hydrolysis was performed with 6 M HCl.

Typical procedure : A THF solution of **1** was added dropwise to a THF solution of the suitable Grignard reagent, cooled at *ca.* -65°C ([RMgX] / [1] = 1.2 / 1). After 30 min. the temperature was raised to 25°C ca. and the hydrolysis was performed according to one of the following procedures: the reaction mixture was poured into a flask containing a stirred solution of: A) 0.2 M HCl at 0°C; B) 0.2 M HCl / THF (4 / 1, v / v); C) 0.1 M HCl, at *ca.* 40°C. After 20 min. the pale blue mixture was extracted into Et₂O. After drying and evaporating the solvent, the crude oil was recovered and purified by Flash Chromatography.

<u>Acknowledgment</u>. This work was supported in part by the Ministero della Ricerca Scientifica e Tecnologica (MURST), Rome and by Consiglio Nazionale delle Ricerche, Progetto Strategico Tecnologie Chimiche Innovative.

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(Received in UK 21 July 1995; accepted 27 October 1995)