Pergamon

Tetrahedron Letters, Vol. 37, No. 22, pp. 3823-3824, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00725-3

New Chemistry of Cyclic, *s-trans*-Enaminones: Addition of Grignard Reagents to Enaminones Derived from 2-Methylcyclohexane-1,3-dione.

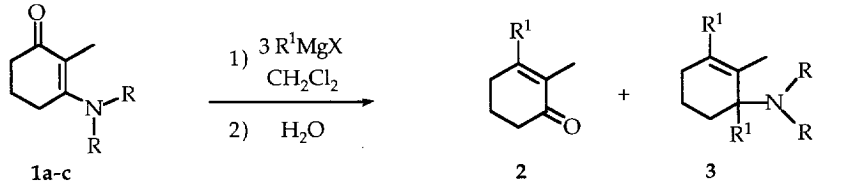
Thomas T. Shawe*, Linda M. Landino, Andrew A. Ross, Anthony S. Prokopowicz, Patrice M. Robinson and Annatina Cannon.

Department of Chemistry, Bucknell University, Lewisburg, PA, 17837.

Abstract: Grignard reagents add to cyclic *s-trans* enaminones to give the cycloalkenone after aqueous hydrolysis. In some cases a competitive double addition takes place. These reactions have been found to be solvent- and reagent-selective.

Cyclic, *s-trans* enaminones have been under active scrutiny for some time.[1] Despite their familiarity, only a single report of the addition of an organometallic reagent has been described, a 1,4 addition-elimination of an alkyllithium in hydrocarbon solvent.[1c] A second reference specifically mentioned the failure of organometallic reagents to add to enaminones derived from 1,3-cyclohexanedione.[1b] Described herein are experiments that demonstrate the viability of adding Grignard reagents to cyclic, *s-trans* enaminones[2] to give cyclohexenones[3] (**2**) in moderate to high isolated yields. In some cases, a disubstituted aminocycloalkene[4] (**3**) is also formed by a novel double addition reaction (Table 1).

Table 1



1a-c **2** **3**

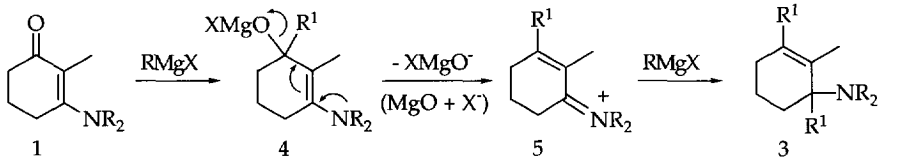
Substrate	R	R^1MgX	Solvent	Yield[a] (2 : 3)
1a	$-CH_2CH_2CH_2CH_2-$	BuMgCl	CH_2Cl_2	47 : 46
1a	$-CH_2CH_2CH_2CH_2-$	BuMgCl	THF	65 : 0[b]
1a	$-CH_2CH_2CH_2CH_2-$	PhMgBr	CH_2Cl_2	64 : 0[c]
1a	$-CH_2CH_2CH_2CH_2-$	EtMgCl	CH_2Cl_2	33 : 65
1a	$-CH_2CH_2CH_2CH_2-$	EtMgCl	THF	55 : 0[b]
1a	$-CH_2CH_2CH_2CH_2-$	EtMgBr	CH_2Cl_2	62 : 15
1b	$-Et_2$	BuMgCl	CH_2Cl_2	36 : 47
1b	$-Et_2$	PhMgBr	CH_2Cl_2	64 : 0[c]
1c	$-CH_2CH_2OCH_2CH_2-$	BuMgCl	CH_2Cl_2	80 : 15
1c	$-CH_2CH_2OCH_2CH_2-$	BuMgCl	THF	84 : 0[b]
1c	$-CH_2CH_2OCH_2CH_2-$	PhMgBr	CH_2Cl_2	90 : 0[c]

Notes: (a) Isolated by chromatography on silica gel. (b) None of the *bis*- adduct **3** was detected. (c) **3**: R^1=Ph has not been characterized.

The product distribution is strikingly solvent- and reagent-specific.[5] In no case was the *bis*- adduct **3** seen in THF. Of further interest is the lack of *bis*-addition of phenylmagnesium bromide. The origins of this solvent- and reagent specificity are currently under investigation.

The cyclohexenones are thought to result from aqueous hydrolysis[6] of **4** (Scheme 1), and formation of the *bis*-adduct suggests 1,2-addition to the carbonyl group with addition of a second RMgX to iminium ion **5**. Although ionization of oxymagnesium halide is unusual, loss of the halide ion would provide a neutral magnesium species. In accord with the proposed mechanism are the reduced yields of **3** from morpholinyl enaminone **1c**, morpholine being the least electron-donating of the three amino groups. This substrate also gave the highest yields of cyclohexenone. Similar multiple additions are observed in hydride reductions and reactions of Grignard reagents with tertiary amides[7a] and lactams,[7b] of which **1** is a vinylogous analogue.

Scheme 1



1 4 5 3

An alternative mechanism involves formation of **5** during aqueous workup, with subsequent addition of unhydrolyzed Grignard reagent.[8] To probe this possibility **1a** was treated with BuMgCl in CH_2Cl_2 according to the normal procedure. The reaction was then quenched by slow addition to rapidly stirring, excess aqueous HCl, followed by basification and extraction into ether. This procedure gave the same ratio of products as experiments in which the reaction was quenched by addition to wet diethyl ether followed by neutralization with 1N aqueous HCl.

Further study of this chemistry is being pursued with the aims of delineating the scope and limitations of the cycloalkenone synthesis, optimizing the formation of the *bis* adduct as alkaloid precursors, and establishing more detailed explanations for the selectivity that is observed.

Acknowledgement: Support for this research was provided by Bucknell University, the Petroleum Research Fund, and Merck & Co. (Summer stipend for PMR). The purchase of a 300 MHz NMR spectrometer was funded by the National Science Foundation (CHE-9122660) and the Keck Foundation.

References:

1. a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277. b) Meyers, A. I.; Reine, A. H.; Gault, R. *J. Org. Chem.* **1969**, *34*, 698. c) Mukaiyama, T.; Ohsumi, T. *Chemistry Lett.* **1983**, 875.
2. a) Iida, H.; Yuasa, Y.; Kibayashi, C. *Synthesis*, **1982**, 471. b) Baraldi, P.G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902.
3. 3-Butyl-2-methyl-2-cyclohexen-1-one: Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 1256. 3-phenyl-2-methylcyclohexen-1-one: Schner, V. F.; Turchin, K. F.; Sheinker, Y. N.; Suvorov, N. N. *Zh. Org. Chem.* **1980**, *16*, 39. 3-Ethyl-2-methyl-2-cyclohexene-1-one: Fukamiya, N.; Oki, M.; Aratani, T. *Chem. Ind. (London)* **1981**, 606.
4. Fully characterized: ^1H, ^{13}C (DEPT), elemental analysis.
5. Typical conditions: RMgX as a solution in diethyl ether was added to a solution of **1** in CH_2Cl_2 or THF at 0 °C; reaction stirred overnight at rt, added to ether, neutralized with 1N HCl, basified with aq. NaOH/NaCl, and extracted into ether. Chromatography on triethylamine-washed silica gel.
6. Stork, G.; Danheiser, R.L. *J. Org. Chem.* **1973**, *38*, 1775., *ref. cit.*
7. a) Kuffner, F.; Satler-Dornbacher, S.; Seifried, W. *Monatsh. Chem.* **1962**, *93*, 469. b) Leonard, N. J.; Hauck Jr., F. P. *J. Am. Chem. Soc.* **1957**, *79*, 5279.
8. Rubottom, G. M.; Kim, C. *J. Org. Chem.* **1983**, *48*, 1550.

(*Received in USA* 11 *March* 1996; *revised* 12 *April* 1996; *accepted* 16 *April* 1996)