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Magnesium/methanol: an effective reducing agent for chemoselective reduction of pyrimidine-2(1*H*)-ones

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ABSTRACT

Magnesium in methanol is an effective reagent for the chemoselective reduction of pyrimidine-2(1*H*)-ones. Other reducible functionalities such as ester and alkene of enamine ester and uriedo carbonyl remain unaffected. This constitutes the first example of the formation of Biginelli 3,4-dihydropyrimidin-2(1*H*)ones through the reduction of pyrimidine-2(1*H*)-ones.

1. Introduction

Biginelli 3,4-dihydropyrimidin-2(1*H*)ones (DHPMs) are known for more than a century.[1] These heterocycles have attracted recent interest owing to their multifaceted pharmacological profiles such as calcium channel modulators,[2] antihypertensive agents,[3] α_{1a}-adrenergic receptor antagonists,[4] mitotic kinesin Eg5 inhibitors,[5] and hepatitis B replication inhibitors.[6] Synthetic manipulation of this important core has yielded[7] a variety of structurally decorated and/or transformed products of immense synthetic consequences. The three-component Biginelli condensation and its uncounted variants have been mainly relied on the availability of acetoacetic ester, aldehyde and urea which sometimes are faced with the limitation of non-availability of the appropriate component required for the synthesis of a particular DHPM derivative bearing that functionality. Our synthetic programme in this direction has relied on the functional elaboration of the basic DHPM core at all possible diversity oriented centres and thus we have been able to decorate N1, N3, C4 and C6 positions following regioselective, site-selective functionalization protocols.[7b–f] However, in the course of a synthetic programme involving the sequence: oxidation of Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) to the corresponding pyrimidine-2(1*H*)-ones (DHPs), transforming C-2 to append various substituents through 2-halopyrimidine derivative and, reduction to the original DHPMs, we required a mild method, tolerant to the substitution variations for the reduction of N3–C4 C=N bond of the precursor pyrimidine-2(1*H*)-one (DHPs). Surprisingly, various methods are available for creating N3–C4 double bond through dehydrogenation[8] using reagents such as HNO_3 or pyridinum chlorochromate, any instance of its reduction through addition of hydride at C4 to obtain DHPMs has not been reported, although in an exclusive example of reduction of ethyl 4-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate using Pt/EtOH and H_2, formation of ethyl 4-methyl-2-oxo-hexahydropyrimidine-5-carboxylate has been reported.[9] Alternatively, 1,4-addition of nucleophiles at C4 position of pyrimidine-2(1*H*)-ones has been reported[7e,10] to obtain C4-substituted DHPMs. With an eye on the vulnerable functionalities around the DHP core, we investigated Mg/MeOH, a mild reagent that has been successfully applied[11] to a number of reductions.

2. Results and discussion

Our results are shown in Table 1. In a typical procedure, the reaction is initiated by the addition of magnesium turnings and a crystal of resublimed iodine to a solution of DHP (**1**) in methanol. Following the disappearance of the starting[8] DHP, the reaction was subjected to an aqueous work-up and the crude products were purified by flash chromatography. The results demonstrate that Mg/MeOH effectively reduces DHPs bearing other reduction-sensitive functionalities. All compounds have been adequately characterized using spectroscopic and other techniques (Supplementary data).

To draw a comparison of this protocol with other commonly used reducing agents, when reduction was attempted with highly

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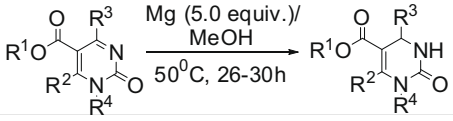
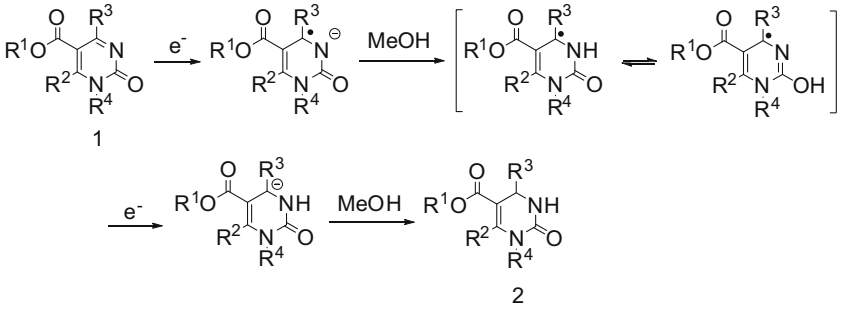
Table 1
Reduction of pyrimidine-2(1*H*)-ones with Mg/MeOH



Entry	DHPs					Biginelli DHPMs						
	1	R^1	R^2	R^3	R^4	**2**	R^1	R^2	R^3	R^4	Time (h)	Yield[a] (%)
1	**1a**	Et	Me	Ph	H	**2a**	Et	Me	Ph	H	24	75
2	**1b**	Me	Me	Ph	H	**2b**	Me	Me	Ph	H	24	64
3	**1c**	Et	Me	Me	H	**2c**	Et	Me	Me	H	26	70
4	**1d**	Me	Me	Me	H	**2d**	Me	Me	Me	H	27	69
5	**1e**	Et	Ph	Me	H	**2e**	Et	Ph	Me	H	24	76
6	**1f**	Et	*n*-Pr	Ph	H	**2f**	Et	*n*-Pr	Ph	H	26	74
7	**1g**	Et	Me	*p*-OMePh	H	**2g**	Et	Me	*p*-OMePh	H	24	70
8	**1h**	Et	Me	Ph	Me	**2h**	Et	Me	Ph	Me	27	62
9	**1i**	Et	Me	*n*-Pentyl	H	**2i**	Et	Me	*n*-Pentyl	H	30	60
10	**1j**	Et	Me	H	H	**2j**	Et	Me	H	H	30	62
11	**1k**	Et	Me	3,4,5-$(OMe)_3C_6H_2$	H	**2k**	Et	Me	3,4,5-$(OMe)_3C_6H_2$	H	27	71

[a] Isolated yields.



Scheme 1. Reductions with Mg/MeOH.

selective sodium cyanoborohydride[12] and other reducing agents such as borohydride[13] and nickel sodium borohydride,[14] under a variety of conditions, unreacted starting DHPs were obtained. It is interesting to note that magnesium/methanol has been implemented in a number of chemical reductions of functionalities such as α,β-unsaturated esters,[11a] peroxides,[11b] benzothiadiazoles,[11c] aziridines,[11d] α,β-conjugated nitriles[11e] and ketones[11f]. However, during the reduction of DHPs, enamine ester as well as uriedo link remains unaffected, thus rendering the protocol highly chemoselective.

The reduction potential of alkali metals is not sufficiently high enough to add two electrons to aliphatic carbonyl group.[15] According to the generally accepted mechanism,[16] protonation of radical anion gives a carbon radical which through its tautomer is subsequently reduced to a carbanion, followed by protonation provides the DHPM **2** (Scheme 1).

In conclusion, we have demonstrated that Mg/MeOH is an effective reagent for the highly chemoselective reduction of pyrimidine-2(1*H*)-one system.

3. Experimental

To a solution of appropriate pyrimidine-2(1*H*)-ones (1 mmol) in MeOH (10 ml) were added freshly scratched Mg turnings (5 mmol) and a tiny crystal of iodine. The resulting solution was warmed to 50 °C until the completion of the reaction (24–30 h). The reaction mixture was poured into cold 0.5 M HCl and extracted with ethyl acetate. The combined ethyl acetate extracts (3 × 10 ml) were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to chromatography on Silica Gel-G (60–120 mesh) with ethyl acetate/hexane (3:7 *v*/*v*) as eluents.

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Supplementary data

References for preparation of starting materials; spectral listings and NMR (^1H and ^{13}C NMR) spectra for the products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.165.

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