Preparation and Reactions of Magnesiated Uracil Derivatives

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Abstract: The I/Mg-exchange of 5-iodouracil derivatives affords the corresponding polyfunctional Grignard reagents which were found to react with various electrophiles in good yields.

Key words: uracil, magnesium, functionalized organometallics, copper

Heterocycles are major molecular building blocks found in many biologically active molecules and their functionalization is an active field of research.¹ Especially useful in this respect are metalated heterocycles and among them many useful lithiated heterocyclic reagents have been prepared.² However due to the highly reactive nature of the carbon-lithium bond, only a few functional groups are tolerated in these heterocycles. Recently, we have shown that a range of zincated polyfunctional heterocycles could be prepared and reacted with electrophiles leading to polyfunctional heterocyclic derivatives.³ Although most organic functional groups could be present on these zincated heterocycles, their moderate reactivity did not allow the reaction with electrophiles like aldehydes or ketones. It was expected that the reactive Grignard reagents would be more appropriate for such reactions combining a good reactivity with a good functional group tolerance. Recently, we have shown that the I/Mg-exchange allows a smooth preparation of polyfunctional aryl,⁴ alkenyl⁵ and pyridyl⁶ magnesium species. Herein, we wish to report that magnesiated uracil derivatives can be readily prepared by this exchange reaction. Thus, the 5-iodouracils **1a-c** respectively substituted at nitrogen with a benzyl group, a ethyloxymethyl group and a 3,5-dimethoxybenzyl group⁷ react with *i*-PrMgBr at -40°C within 45 min affording the corresponding Grignard reagents 2a-c which are perfectly stable at this temperature for several hours. The reaction of **2a-c** with various electrophiles (aldehyde, ketone, immonium salt or allylic bromide) proceeds smoothly furnishing various new 5-substituted uracil derivatives of type **3** (Scheme and Table 1).

Whereas aromatic and aliphatic aldehydes undergo a smooth addition leading to the heterocyclic benzylic alcohols **3a-d** (see entries 1-4 of Table 1), the addition of ketones like cyclohexanone proved to be more sluggish leading to the tertiary alcohol **3g** in only 45 % yield (see entry 7). The reaction with the immonium trifluoroacetate $(CH_2=N(Allyl)_2^+, CF_3CO_2^-)^8$ furnishes the expected aminomethyl derivatives **3e-f** in excellent yields (see entries 5 and 6). The electrophilic cyanation reagent TolSO₂CN reacts with the magnesiated uracil **2a** providing the 5-cyanouracil derivative **3h** in 47 % yield (see entry 8). After





a transmetalation to the corresponding copper derivative with CuCN-2LiCl,⁹ a benzoylation with PhCOCl gives the ketone **3i-j** in 73-75% yield. Finally the allylation with ethyl (2-bromomethyl)acrylate¹⁰ leads to the desired allylated products **3k-l** in 76-83 % yield (entries 11-12).

In summary, we have prepared magnesiated uracils via an iodine-magnesium exchange and have shown its excellent reactivity with various electrophiles leading to uracil derivatives having potential biological properties.¹¹ Extension of these reactions is currently underway in our laboratories.

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References and Notes

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Entry	Mg- Uracils of type 2	Electrophile	Product of type 3	Yield (%) ^a
1 2	2a 2c	PhCHO PhCHO	$3a : R = Bn$ $3b : R = 3.5 - diMeOC_6H_3$ $R = 0 + n + hex$	80 83
3 4	2a 2b	n-HexCHO n-HexCHO	$3c: R = Bn$ $3d: R = EtOCH_2$	77 74
5 6	2a 2b	CH ₂ =N(allyl) ₂ * CF ₃ CO ₂ *	$3e: R = Bn$ $3f: R = EtOCH_2$	85 82
7	2a	cyclohexanone		45
8	2a	p-TolSO₂CN		47
9 10	2a 2b	PhCOCI PhCOCI	3i : R = Bn $3j : R = EtOCH_2$ $R = CO_2Et$	73 ^b 75 ^b
11 12	2b 2c	ethyl (2-bromo- methyl)acrylate 	$O' \cap N'$ R 3k : R = Bn $3l : R = EtOCH_2$	76° 83°
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 Table 1 Products 3a-l obtained by the reaction of the magnesiated uracils 2a-c with electrophiles.

^aIsolated yield of analytically pure product. ^bA stoechiometric amount of CuCN-2LiCl was added prior to the addition of PhCOCl. ^cA catalytic amount of CuCN (10 mol%) was added prior to the addition of the allylic bromide.

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- (11) **Typical procedure:** *Preparation of 5-(2-carbethoxy-2-propenyl) N, N-dibenzyluracil* (**3k**; entry 11 of Table 1). A dry three necked flask equipped with a magnetic stirring bar, a thermometer and a septum was charged with 5-iodo-N,N-dibenzyluracil (**1a**; 1.3 g, 3.1 mmol) in THF (3 mL) and cooled to $-40 \text{ }^\circ\text{C}$. *i*-PrMgBr (3.4 mL, 3.4 mmol, 1M in THF) was dropwise added and the reaction mixture was stirred at $-40 \text{ }^\circ\text{C}$ for 45 min. CuCN (28 mg, 0.3 mmol) was added followed by ethyl (2-bromomethyl)acrylate (675 mg, 3.5 mmol). The reaction mixture was stirred 1h at -40°C, then allowed to warm to 0 °C and worked up as usual. The crude residue obtained after evaporation of the solvents was purified by flash-chromatography (pentane: ether = 6 : 4) yielding the pure product **3k** (954 mg, 76 % yield) as a colorless oil.

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