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Deprotonation of furans using lithium magnesates

Florence Mongin,^{a,*} Aurélien Bucher,^a Jean Pierre Bazureau,^a Omar Bayh,^b Haçan Awad^b and François Trécourt^b

^aSynthèse & ElectroSynthèse Organiques, UMR CNRS 6510, Bâtiment 10A, Université de Rennes 1, Campus de Beaulieu, Avenue du Général Leclerc, 35042 Rennes Cedex, France

^bLaboratoire de Chimie Organique Fine et Hétérocyclique, UMR CNRS 6014, IRCOF, Université et INSA de Rouen, Place E. Blondel, BP 08, 76131 Mont-Saint-Aignan Cedex, France

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Abstract—Furan was deprotonated on treatment with 1/3 equiv of Bu_3MgLi in THF at rt. The lithium arylmagnesate formed was either trapped with electrophiles or involved in a palladium-catalyzed cross-coupling reaction with 2-bromopyridine. The highly coordinated magnesate Bu_4MgLi_2 (1/3 equiv) proved to be a better deprotonating agent than Bu_3MgLi ; the monitoring of the reaction using NMR spectroscopy showed that the deprotonation of furan at rt required 2 h whereas the subsequent electrophilic trapping was instantaneous. The method was extended to benzofuran, allowing its functionalization at C2 in high yields. The deprotonation of 2-methylfuran and lithium furfurylalkoxide at C5 turned out to be difficult, requiring either long reaction times or higher temperatures.

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We describe the first magnesates in the furan series.

The preparation of heteroaromatic structures is an important synthetic goal because of the multiple applications of these molecules.¹ Deprotonation reaction using lithiated bases has been developed as one of the major tools to functionalize heterocycles.² Nevertheless, this methodology often requires low temperatures, which can be difficult to realize on an industrial scale. In addition, unlike organoboron, organotin, organozinc, and organomagnesium compounds, organolithiums can hardly be directly involved in cross-coupling reactions.³

Deprotonation reactions of heterocycles using magnesiated bases⁴ have been less extensively explored. The pioneering work of Marxer and Siegrist in 1974 showed that EtMgBr was capable of deprotonating 1-phenylpyrazole at the *ortho* position of the phenyl ring.⁵ Schlecker reported in 1995 the regioselective magnesiation of pyridine carboxamides and carbamates with Hauser bases (DAMgBr, DA = diisopropylamino, or TMPMgBr, TMP = 2,2,6,6-tetramethylpiperidino) or magnesium diamides (DA₂Mg or TMP₂Mg);⁶ alkylmagnesium halides and dialkylmagnesiums rarely deprotonate such substrates because of easier 1,4-addition reactions.⁷ More recently, Kondo and Sakamoto described the regioselective magnesiation of *N*-substituted indoles,⁸ thiophenes,⁹ and thiazole⁹ using DA₂Mg, DAMgBr, and DAMgCl. Nevertheless, because of the limited reactivity of these bases, an excess has in general to be used to ensure good yields. Pyrrole rings of numerous 1-phenyldipyrromethanes did not require protection step to be deprotonated at the position adjacent to the nitrogen atom using EtMgBr.¹⁰

In 1999, Kondo achieved the deprotonation of pyridine and its bromo derivatives, quinoline, isoquinoline, and ethyl thiophenecarboxylates through the formation of an arylzincate using lithium di-*tert*-butyl(2,2,6,6-tetramethylpiperidino)zincate as a base.¹¹

Due to a more covalent carbon–metal bond, organozinc derivatives are less reactive than organomagnesium compounds.¹² Since zincates 'softly' react with electrophiles,¹³ we have therefore been interested in the synthesis of 'harder' arylmagnesates¹⁴ using deprotonation reactions. Since 1999, Mulvey has documented the preparation of mixed-metal sodium–magnesium or potassium–magnesium amides for the site selective deprotonation of benzene,¹⁵ toluene,¹⁶ ferrocene,¹⁷

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^{*} Corresponding author. Tel.: +33 (0) 2 23 23 69 31; fax: +33 (0) 2 23

^{23 63 74;} e-mail: florence.mongin@univ-rennes1.fr

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Scheme 1.



Herein, we describe the first deprotonation reactions of furans using magnesates, and the reactivity of the furan magnesates toward electrophiles or in palladium-catalyzed cross-coupling reactions with aryl halides.

Furan (1) can be readily metalated in high yields at C2 by reaction with BuLi in refluxing diethyl ether for 4 h,²⁵ but the use of this base, without²⁶ or with²⁷ TME-DA, in tetrahydrofuran (THF) at temperatures between $-75 \,^{\circ}C^{26}$ and room temperature $(rt)^{27}$ is effective too.

The deprotonation of furan (1) was attempted using 1/3equiv of lithium tributylmagnesate¹⁴ (Bu₃MgLi) in THF at rt. Addition to the reaction mixture of iodine or 3,4,5-trimethoxybenzaldehyde after 2 h afforded iodide 2a and alcohol 2b, respectively, in good yields. The intermediate magnesate of furan was next involved in cross-coupling with 2-bromopyridine under palladium catalysis using 1,1'-bis(diphenylphosphino)ferro-cene (dppf) as ligand,^{23,28} to give biaryl compound **3** in 64% yield (Scheme 1).

Since dilithium tetramethylzincate exhibits a higher reactivity than lithium trimethylzincate in various reactions including halogen-metal exchange,13 Bu₃MgLi (1/3 equiv) and dilithium tetrabutylmagnesate (Bu₄-MgLi₂, 1/3 equiv)²⁹ were compared as deprotonating agents. The highly coordinated lithium magnesate proved to be the most efficient base: trapping the reaction mixture by iodine or 3,4,5-trimethoxybenzaldehyde after 2 h furnished iodide 2a and alcohol 2b in 90% and 85% yields, respectively, against 75% and 72% using Bu₃MgLi.

The reaction using Bu₄MgLi₂ was monitored by recording ¹H NMR spectra of the reaction mixture.³⁰ The increasing of signals at 7.81 (d), 6.62 (d), and 6.37 (dd) ppm attributed to the hydrogens at the 5, 3, and 4 positions of the magnesiated furan, respectively, showed that furan was slowly deprotonated to reach a 95% conversion after 1.5 h. Thiophene being completely deprotonated in 15 min using 1/3 equiv of Bu₃MgLi-TMEDA²³ in THF at rt, reactions involving furan were attempted using Bu₃MgLi·TMEDA or Bu₄MgLi₂· TMEDA, but without significant improvement. The signals associated with the magnesiated furan instantly decreased upon addition of 3,4,5-trimethoxybenzaldehyde (1 equiv) to the reaction mixture. Benzophenone and chlorodiphenylphosphine were also successfully used as electrophiles to give alcohol 2c and phosphine 2d in good yields (Scheme 2).

These conditions were tested to metalate less activated furans such as 2-methylfuran (4). Lithiation of 2-alkylated furans has been reported using BuLi in THF at temperatures between -78^{31} and 0 °C.³² The reaction of 2-methylfuran (4) with Bu_4MgLi_2 (1/3 equiv) in THF was monitored as before (the signals at 6.0 and 6.7 ppm were attributed to the hydrogens at the 3 and 4 positions of the 5-magnesiated 2-methylfuran). It was observed that the reaction was very slow at rt, with metalated and non-metalated species in ratios of 60:40, 70:30, and 75:25, after 2, 4, and 30 h, respectively. Heating the reaction mixture at reflux for 1 h resulted in a 85:15 ratio while quenching with ClPPh₂ afforded phosphine 5 in 39% yield (Scheme 3).

Ring deprotonation of furfuryl alcohol (6) was studied next. 4-(2-Furyl)butan-1-ol being dideprotonated by using simply 2 equiv of the chelate BuLi-TMEDA in diethyl ether at rt for 1 h,³³ the use of 1/2 equiv of Bu₄MgLi₂ was first attempted, but without success. Since lithium alkoxides hardly react with diorganomag-







Scheme 4.

nesiums in chelating/polar solvents,³⁴ one can imagine that dilithium dibutyldi(furfurylalkoxo)magnesate, if formed after the alcohol function deprotonation, rapidly evolves toward lithium furfurylalkoxide and dibutyl-magnesium, the latter being unable to deprotonate the furan ring (Scheme 4).

It was thus decided to attempt the deprotonation of the lithium salt of **6** using 1/3 equiv of Bu₄MgLi₂ in THF at rt. After 2 h, the reaction mixture was quenched with heavy water to give the deuterated compound 7 in a moderate yield (Scheme 5).

Since lithium magnesates did not prove to be efficient enough for the deprotonation of 2-methylfuran and lithium furfurylalkoxide, we attempted to deprotonate more activated ethyl 2-furoate or ethyl 2-thiophenecarboxylate using Bu_4MgLi_2 (1/3 equiv), Bu_3MgLi (1/3 equiv) or else less nucleophilic DA_3MgLi^{35} (1/3 equiv), but without success.³⁶ These failures could be due to the presence of the ester function.

The reaction was next extended to benzofuran (8). The latter is usually deprotonated in THF at -78 °C using either lithium dialkylamides³⁷ or alkyllithiums.³⁸ Under

1 eauiv BuL

THF. rt

 1/3 equiv Bu₄MgLi₂

THF, rt, 2 h

D₂O

7.48%

yields, ranging from 85% to 89%. Even if cross-couplings using dilithium tetra(2-furyl)zincates have been reported to proceed in slightly lower yields than those using lithium tri(2-furyl)zincates,³⁹ we attempted reactions of the higher order benzofuran magnesate, Bu(2-benzofuryl)₃MgLi₂,⁴⁰ with aromatic halides under palladium catalysis. The use of PdCl₂(dppf)^{23,28} at THF reflux allowed the reactions with iodobenzene and 2-bromopyridine to produce compounds **10a** and **10b** in 66% and 58% yields, respectively (Scheme 6).

the conditions optimized for furan, iodide 9a, alcohols

9b, and 9c, and phosphine 9d were provided in high

In conclusion, Bu_4MgLi_2 proved to be more efficient than Bu_3MgLi for the deprotonation of furan in THF at rt. It was shown using NMR spectroscopy that the deprotonation step required 2 h whereas the subsequent trapping with electrophiles was instantaneous. The method was very nicely transposed to benzofuran, giving 2-functionalized derivatives in high yields. Lithium magnesates were not efficient enough for the deprotonation of less activated 2-methylfuran and furfuryl alcohol; the long reaction times or reflux required in this case are of limited scope.

Lithium magnesates are suitable for hydrogen-magnesium exchange reactions on furan and benzofuran at rt, whereas the corresponding hydrogen-lithium exchanges have sometimes to be performed at lower temperatures. Unlike the corresponding lithio compounds, the furan magnesium ate complexes here obtained are enough stable to undergo cross-coupling reactions without the need for conversion to organoboron, organotin, or organozinc derivatives.



Scheme 5.

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Supplementary data

Experimental procedures and analyses of compounds are furnished. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.066.

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