An Unprecedented Coupling Reaction of Arylmagnesium Compounds with Tetrahydrofuran Providing 2-Aryltetrahydrofuran Mediated by an Iodoalkane-EtMgBr System

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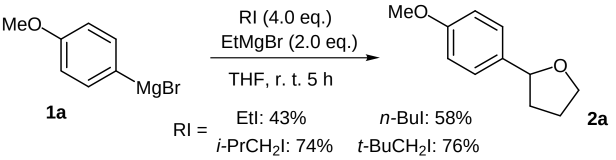
Abstract: An extremely facile coupling reaction between arylmagnesium compounds and THF by means of an iodoalkane–EtMgBr system provides 2-aryltetrahydrofurans. One-pot synthesis of 2-thienyltetrahydrofuran is achieved from thiophene and THF using this coupling reaction.

Key words: coupling, iodine, magnesium, radical reactions, tetrahydrofuran

Grignard reagents are an indispensable synthetic tool for organic chemists and are frequently used in the laboratory. Additionally, numerous industrial applications have been also reported.[1] Their main reaction patterns can be classified into (1) nucleophilic addition or substitution, (2) proton abstraction as a base, and (3) magnesium–halogen exchange reaction.[2] In addition, some reactions involving single electron transfer from Grignard reagents to organic molecules such as carbonyl compounds or alkyl halides are also reported.[3] Synthetic applications of the reaction of this fourth type, however, have been quite limited so far.[4] Here we wish to report an unprecedented conversion of arylmagnesium compounds into 2-aryltetrahydrofurans[5] via a single electron transfer reaction mediated by an iodoalkane-EtMgBr[6] system.

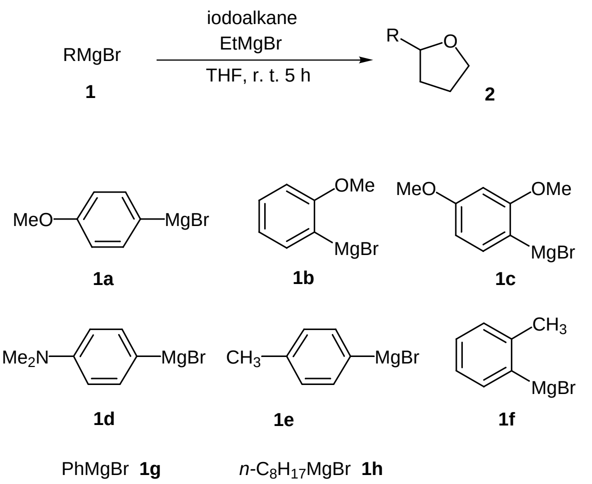
To a THF solution of 4-methoxyphenylmagnesium bromide (**1a**), EtI (4.0 eq.) and EtMgBr (2.0 eq.) were added and the resulting mixture was stirred for 5 h at 25 ° C. Aqueous workup afforded 4-(2-tetrahydrofuryl)anisole (**2a**) in 43% yield. Use of a more sterically hindered iodoalkane, which could hardly react with EtMgBr via an S_N2 process, such as *i*-$PrCH_2I$ or *t*-$BuCH_2I$ in place of EtI improved the yield of **2a** to 74% or 76%, respectively (Scheme 1).[7] The reaction proceeded very cleanly to give only **2a** and anisole without contamination by any byproducts.



Scheme 1

The generality of this coupling reaction with THF was examined using various Grignard reagents. The results are summarized in Table 1. The reaction with electron-rich arylmagnesium reagents **1a**, **1b**, and **1c** afforded the corresponding products in good yields (entries 1, 2 and 3). The use of dimethylaminophenylmagnesium **1d** decreased the yield (49%, entry 4). Unfortunately, tolyl (**1e** or **1f**), phenyl (**1g**), or *n*-octyl (**1h**) Grignard reagent gave the desired coupling product in poor yield under the same reaction conditions.

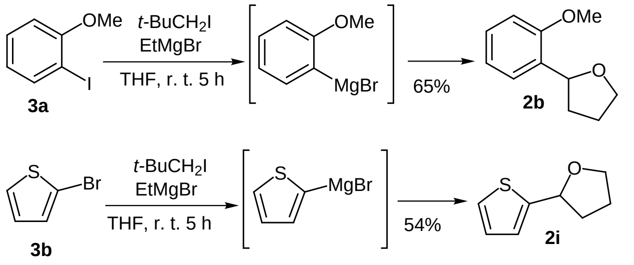
Table 1 Coupling Reaction of Grignard reagents with THF.[a)]



Entry	R	Iodoalkane	Equiv of EtMgBr	Yield(%)
1	**1a**	*t*-$BuCH_2I$ (4 eq.)	2 eq.	76
2	**1b**	*t*-$BuCH_2I$ (6 eq.)	3 eq.	66
3	**1c**	*i*-$PrCH_2I$ (4 eq.)	2 eq.	78
4	**1d**	*i*-$PrCH_2I$ (4 eq.)	2 eq.	49
5	**1e**	*t*-$BuCH_2I$ (6 eq.)	3 eq.	37
6	**1f**	*t*-$BuCH_2I$ (6 eq.)	3 eq.	23
7	**1g**	*t*-$BuCH_2I$ (6 eq.)	3 eq.	12
8	**1h**	*i*-$PrCH_2I$ (4 eq.)	2 eq.	27

a) All reactions were carried out at 25 ° C for 5 h.

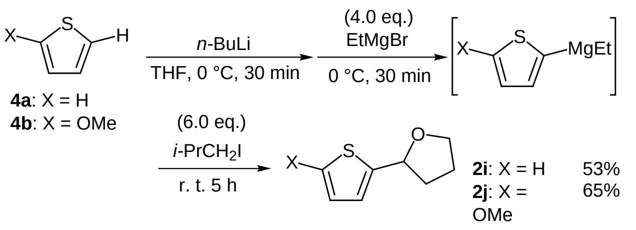
It is well known that arylmagnesium compounds can be easily prepared via halogen–magnesium exchange reaction. Thus, it is anticipated that aryl halides could be converted into arylated tetrahydrofurans in one-pot. This was indeed the case and treatment of 2-iodoanisole (**3a**)[8] or 2-bromothiophene (**3b**)[9] with EtMgBr and *t*-BuCH$_2$I in THF provided **2b** or **2i** in 65% or 54% yields, respectively (Scheme 2).



EtMgBr (4.0 eq.) and *t*-BuCH$_2$I (6.0 eq.) were employed.

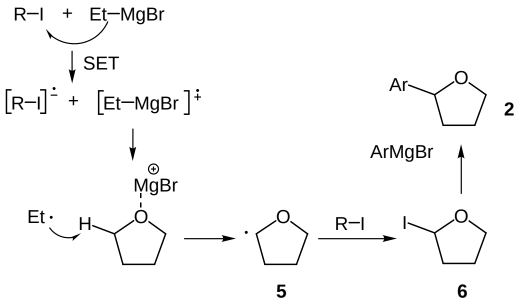
Scheme 2

Alternatively, thiophene itself could be used as a starting material. Metallation of thiophene with butyllithium[10] followed by an addition of excess amount of EtMgBr (4.0 eq.) provided 2-magnesiothiophene. An addition of *i*-PrCH$_2$I afforded 2-(2-thienyl)tetrahydrofuran in good yield (Scheme 3).[11] This is also a one-pot reaction which provides a new synthetic route to 2-aryltetrahydrofurans from aromatic compounds and THF.



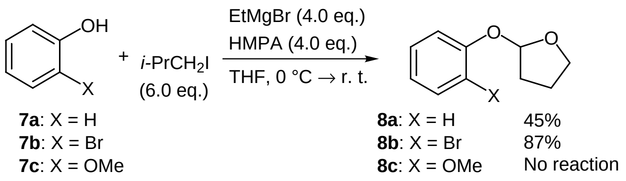
Scheme 3

Although the reaction mechanism has not been clarified at this stage, a possible mechanism might be envisaged as shown in Scheme 4. Single electron transfer from EtMgBr to iodoalkane would provide an ethyl radical which could abstract a hydrogen on C2 carbon of THF.[12] The resulting 2-tetrahydrofuryl radical **5** would attack the iodoalkane to give 2-iodotetrahydrofuran **6**[13] which would be converted into arylated product **2** by the action of the arylmagnesium compound. Since *i*-PrCH$_2$I or *t*-BuCH$_2$I would not be wasted via an anionic S$_N$2 process, the radical process could proceed effectively in the case of the reaction using these iodides.



Scheme 4

The intermediacy of iodotetrahydrofuran **6** could be ascertained by the following experiment (Scheme 5). Treatment of 2-bromophenol (**7b**) with EtMgBr and *i*-PrCH$_2$I in the presence of HMPA afforded the 2-(2-bromophenoxy)tetrahydrofuran (**8b**) in 87% yield. An addition of HMPA was essential in the reaction with phenoxide and only a trace amount of **8** was formed in the absence of HMPA.



Scheme 5

Acknowledgement

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(14) **Representative experimental procedure:** To a solution of 4-methoxyphenylmagnesium bromide (0.94 mL, 1.06 M THF solution, 1.0 mmol) in THF (3 mL), neopentyl iodide (0.79 g, 4.0 mmol) and EtMgBr (2.0 mL, 1.01 M THF solution, 2.0 mmol) were added at 25° C under argon atmosphere. After 20 min, a white precipitate was formed. The mixture was stirred for 5 h. Then, saturated aqueous NH_4Cl (20 mL) was added to the reaction mixture carefully and the whole was extracted with hexane (10 mL X 3). Concentration and purification by silica-gel column chromatography afforded 4-(2-tetrahydrofuryl)-anisole (**2a**, 135 mg, 0.76 mmol) in 76% yield: IR (neat) 2932, 2862, 1613, 1587, 1509, 1460, 1364, 1302, 1243, 1174, 1058, 1038, 919, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71-1.85 (m, 1 H), 1.89-2.09 (m, 2 H), 2.20-2.32 (m, 1 H), 3.78 (s, 3 H), 3.90 (ddd, J = 6.6, 8.0, 8.0 Hz, 1 H), 4.07 (ddd, J = 6.9, 8.0, 8.0 Hz, 1 H), 4.82 (dd, J = 7.2, 6.9 Hz, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.26 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.67, 34.13, 54.80, 68.08, 80.13, 113.42, 126.73, 135.15, 158.68. Found: C, 74.29; H, 8.06. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92.

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