

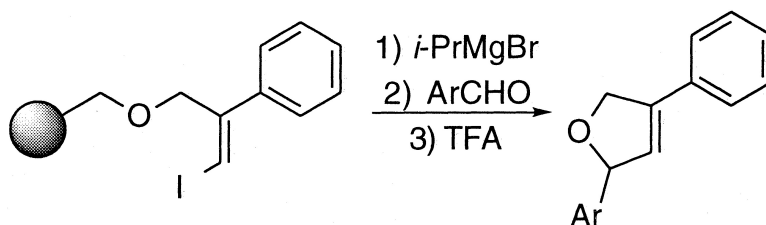
Report

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Ar = aromatic or heteroaromatic rest

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Synthesis of 2,4-Disubstituted 2,5-Dihydrofurans and 1-Substituted 1,3-Dihydroisobenzofurans via an Iodine–Magnesium Exchange Reaction

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While translating solution phase organic carbon–carbon coupling reactions into solid phase organic chemistry one often experiences a decrease in reactivity due to the heterogeneity of the reaction and therefore elongated reaction times and/or incomplete reactions. To overcome these problems the use of highly reactive organometallic intermediates could be helpful. Functional group tolerance and relative reactivity are crucial for the generation of a maximum of diversity in combinatorial chemistry. Organozincates have been generated on a resin leading to polyfunctional organometallics with moderate reactivity.¹ Grignard reagents represent a well-established class of organometallic reagents with high reactivity toward many electrophiles but they could not be prepared when functional groups such as esters, amides, or nitriles were present.² The halogen–magnesium exchange reaction constitutes one possible access to Grignard reagents.³ Lately, we have found reaction conditions which allow the preparation of highly functionalized aryl Grignard compounds employing a low-temperature iodine–magnesium exchange reaction.⁴ Herein, we present general reaction conditions for the formation of resin-bound aryl- and alkenyl-magnesium compounds starting from resin-bound iodides and their reaction with aromatic aldehydes, as well as a cyclization–cleavage approach under mild conditions to yield 2,5-dihydrofurans and 1,3-dihydroisobenzofurans.

As starting material, trichloroacetimidate resin **1** was prepared from Wang resin⁵ using standard literature procedure.⁶ It was reacted in parallel synthesis with reagent chemset **2** (Figure 1, Scheme 1) to furnish resin-bound chemset **3** containing two (*Z*)-alkenyl iodides (**3**{*1*–*2*})⁷ and an aryl iodide (**3**{*3*}) (Figure 2)). Test cleavage of chemset **3** using TFA (10% in CH₂Cl₂) revealed a ca. 90% conversion of Wang resin and a purity of >95%, as determined by mass recovery and HPLC analysis of reisolated **2**. Each compound **3**{*1*–*3*} was then subjected to an iodine–magnesium exchange reaction by treatment with *i*-PrMgBr (ca. 10 equiv) in a solvent mixture of THF/NMP (40:1) at –40 °C. The exchange reaction was monitored by quenching of **4**{*1*} with THF/H₂O/AcOH (80:15:5) and subsequent TFA cleavage as above. After 1.5 h reaction time no more alkenyl iodide could be detected by HPLC analysis. In THF without a cosolvent,⁴

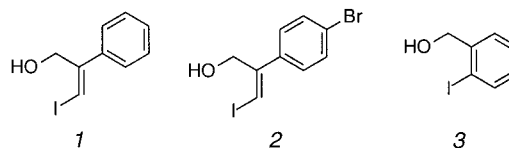


Figure 1. Reagents **2**{*1*–*3*}.

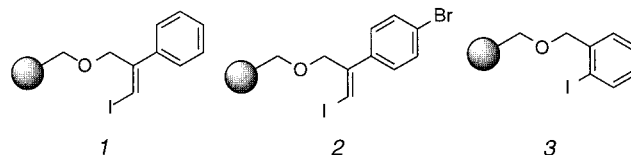
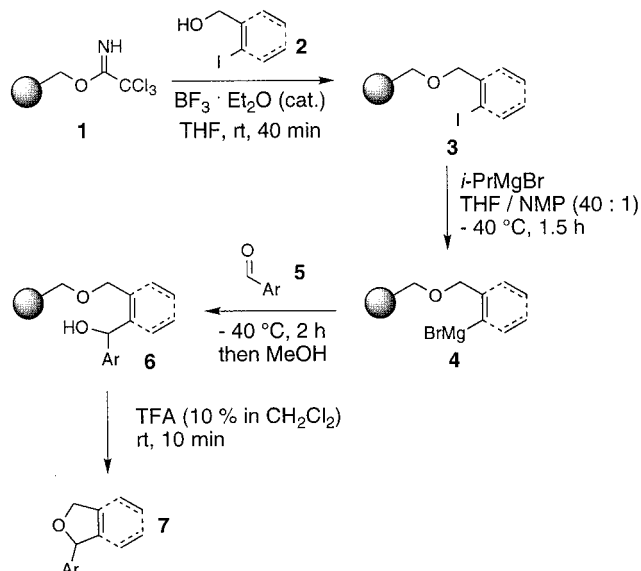


Figure 2. Structures of resin-bound iodides **3**{*1*–*3*}.

Scheme 1



however, quenching of **4**{*1*} after 2 days at –40 °C still revealed >5% starting iodide **2**{*1*}, clearly demonstrating an acceleration of the iodine–magnesium exchange reaction by NMP.⁸ In the case of **3**{*2*} no bromine–magnesium exchange product could be detected, showing the selectivity of the iodine–magnesium exchange reaction. The chemset **4** was then reacted in parallel synthesis with reagent chemset **5** (ca. 15 equiv, Scheme 1 and Figure 3) at –40 °C for 2 h, followed by quenching of the reaction mixture at low temperature with wet MeOH, affording resin-bound chemset **6**. All members of chemset **6** were treated with TFA (10% in CH₂Cl₂, 10 min), affording soluble product chemset **7** (Scheme 1 and Table 1). Part of the scope of this reaction was demonstrated by using aromatic aldehydes bearing several functional groups with different electronic properties. Electron rich aromatic aldehydes (**5**{*2*–*4*}, **5**{*7*–*9*}) were as well suited for this synthetic method as electron deficient aromatic aldehydes (**5**{*5*–*6*}), furnishing the substituted and functionalized 2,5-dihydrofurans **7**{*1*–*2*,*2*–*9*} and 1,3-dihydroisobenzofurans **7**{*3*,*2*–*9*}. Remarkably, even an aldehyde containing a nitro group (**5**{*10*}) was tolerated in this reaction, and the nitro-substituted 2,5-dihydrofurans **7**{*1*–*2*,*10*} and 1,3-dihydroisobenzofuran **7**{*3*,*10*} could be isolated in satisfactory to good yields and good purities.

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Table 1. 2,4-Disubstituted 2,5-Dihydrofurans 7{1-2,1-10} and 1-Substituted 1,3-Dihydroisobenzofurans 7{3,1-10} Derived by an Iodine-Magnesium Exchange Reaction on Resin-Bound Iodides 3 Followed by Subsequent Reaction with Aldehydes 5 and Cyclization-Cleavage Reaction

iodide 3	alde- hyde 5	product 7	purity (%) ^a (yield (%) ^b)	iodide 3	alde- hyde 5	product 7	purity (%) ^a (yield (%) ^b)
3{1}	5{1}	7{1,1}: R=Ph	98 (89)	3{3}	5{4}	7{3,4}	93 ^c (69)
3{2}	5{1}	7{2,1}: R= <i>p</i> -BrPh	98 (90)				
3{3}	5{1}	7{3,1}	93 ^c (95)	3{1}	5{5}	7{1,5}: R=Ph	99 (79)
				3{2}	5{5}	7{2,5}: R= <i>p</i> -BrPh	97 (87)
3{1}	5{2}	7{1,2}: R=Ph	92 (83)	3{3}	5{5}	7{3,5}	95 (91)
3{2}	5{2}	7{2,2}: R= <i>p</i> -BrPh	97 (81)				
3{3}	5{2}	7{3,2}	95 ^c (93)	3{1}	5{6}	7{1,6}: R=Ph	98 (90)
				3{2}	5{6}	7{2,6}: R= <i>p</i> -BrPh	99 (88)
3{1}	5{3}	7{1,3}: R=Ph	98 (65)	3{3}	5{6}	7{3,6}	92 (98)
3{2}	5{3}	7{2,3}: R= <i>p</i> -BrPh	99 (86)				
3{3}	5{3}	7{3,3}	96 (90)	3{1}	5{7}	7{1,7}: R=Ph	97 (87)
				3{2}	5{7}	7{2,7}: R= <i>p</i> -BrPh	96 (88)
3{1}	5{4}	7{1,4}: R=Ph	81 (55)	3{3}	5{7}	7{3,7}	99 (95)
3{2}	5{4}	7{2,4}: R= <i>p</i> -BrPh	95 (68)				

Table 1 (Continued)

iodide 3	alde- hyde 5	product 7	purity (%) ^a (yield (%)) ^b	iodide 3	alde- hyde 5	product 7	purity (%) ^a (yield (%)) ^b
3{1}	5{8}	7{1,8}: R=Ph	89 (71)				
3{2}	5{8}	7{2,8}: R=p-BrPh	86 (67)	3{3}	5{9}	7{3,9}	96 ^c (98)
3{3}	5{8}	7{3,8}	93 (79)	3{1}	5{10}	7{1,10}: R=Ph	91 (70)
				3{2}	5{10}	7{2,10}: R=p-BrPh	92 (64)
3{1}	5{9}	7{1,9}: R=Ph	98 (94)				
3{2}	5{9}	7{2,9}: R=p-BrPh	96 (95)	3{3}	5{10}	7{3,10}	93 (81)

^a HPLC purity (RP-C18, MeCN/H₂O (0.1% TFA) gradient 5–100% MeCN, UV detection at 254 nm). ^b Recovered material of indicated purity. ^c UV detection at 215 nm.

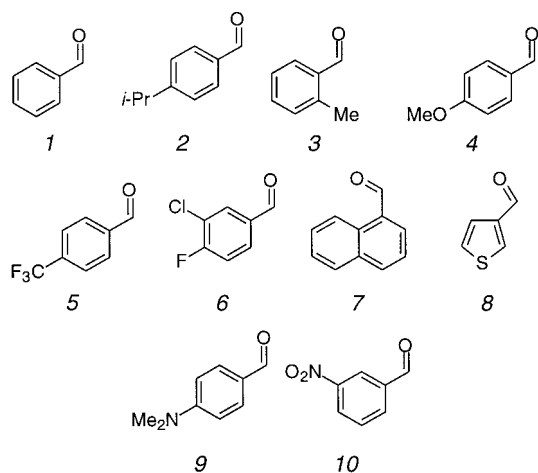


Figure 3. Reagents 5{1–10}.

In conclusion, we have shown that the iodine–magnesium exchange reaction is a mild method for the preparation of resin-bound aryl and alkenyl Grignard reagents. We have evaluated this by the synthesis of a library (30 compounds) of various substituted 2,5-dihydrofurans and 1,3-dihydroisobenzofurans. Investigations on the scope of this synthesis and on combining this technique with transition metal catalyzed cross-coupling reactions are currently underway.

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Supporting Information Available. General experimental procedures, characterization data, and ¹H NMR and ¹³C NMR spectra of selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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