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A GENERAL, CONVENIENT AND HIGHLY EFFICIENT SYNTHESIS OF DIARYLMETHANES BY COPPER-CATALYZED REACTION

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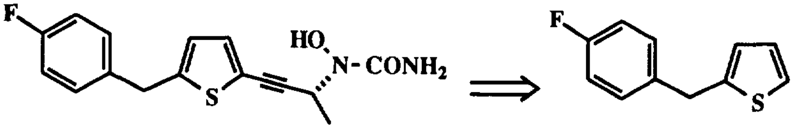
Abstract: Copper-catalyzed reactions of arylmagnesium derivatives with benzyliodides have been developed for the large scale preparation of diarylmethanes. Various diarylmethanes have been prepared in high yield by this reaction, the amount of homocoupled dimers being less than 3%.

One of the research areas Abbott Laboratories focuses on is the development of new classes of 5-lipoxygenase inhibitors. [1, 2] 5-Lipoxygenase is the first dedicated enzyme in the pathway leading to the biosynthesis of leukotrienes.[3] Leukotrienes play an important role in various allergic and inflammatory diseases including asthma, allergic rhinitis, rheumatoid arthritis, and inflammatory bowel disease. [4] ABT-761 **1**, [5] discovered at Abbott, is a very potent 5-lipoxygenase inhibitor. Our research efforts have been directed toward an efficient synthesis of **1**.

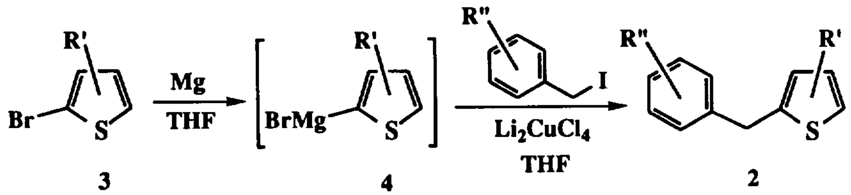


1 **2**

2-(4'-fluorobenzyl)thiophene **2** is a key intermediate in the synthesis of **1**. Rapid advancement of the new inhibitor in clinical trials necessitated quick preparation of multi-kilo quantities of 2-(4'-fluorobenzyl)-thiophene. A large scale chemical processes should be reproducible, scaleable, and economically efficient. It should address issues such as the availability of raw materials, throughput, safety, and waste treatment. During the course of development, several literature approaches were evaluated. All of them suffered from some fatal flaw for large-scale preparation. For example: 1) Traditional lithiation of thiophene followed by benzylation with benzylbromide [6] requires cryogenic reaction conditions and produces low purity product. 2) Kumada's Nickel-phosphine complex catalyzed Grignard coupling of aryl halides and benzyl Grignards [7] only worked well in diethyl ether, which is a significant fire hazard and can not be used in the pilot plant. When other solvents were used, large amounts of dimers were formed. 3) Friedel-Crafts benzylation [8] gave unreproducible results. It often produces a mixture of 2- and 3-alkylation regioisomers. [9] The disadvantages of these approaches have limited their use for large scale production of **2**.

In this communication, we wish to report a general, convenient, and highly efficient synthesis of diarylmethanes *via* a copper-catalyzed reaction of arylmagnesium derivatives with benzyliodides. Thienylmagnesium bromide prepared from bromothiophene and magnesium metal reacted with various benzyliodides in the presence of catalytic amounts of Li_2CuCl_4 [10] in THF at room temperature, forming diarylmethanes in high yield (Scheme I, Table I). It was found that the electronic nature of the substituent on the benzene ring of the benzyliodides has very little effect on the coupling reaction; i.e. benzyliodides with both electron-withdrawing (entries 2-4) or electron-donating (entries 5-6) groups underwent smooth coupling reactions with thienymagnesium bromide under mild conditions. It was also found that the reactions went well in a broad range of temperatures, from 0°C to 45°C, forming homocoupled products in less than 3%. Similarly, 3-methyl-2-thienylmagnesium bromide prepared from 3-methyl-2-bromothiophene also reacted smoothly with benzyliodides (entries 7-8).

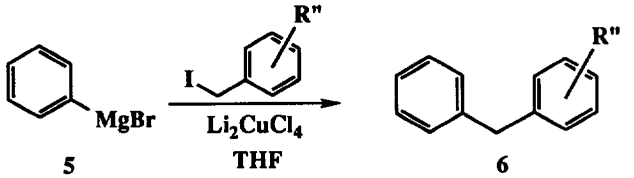
Scheme I



Phenylmagnesium bromide prepared from bromobenzene also reacted as efficiently with various benzyliodide derivatives to form a variety of dibenzyl derivatives in high yield (Scheme II, entries 9-10).

The benzyliodides can be easily obtained from the reaction of corresponding chlorides with NaI in THF at reflux temperature. The product mixture can be used directly in the coupling reaction without work-up. The excess NaI does not interfere with the reaction.

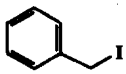
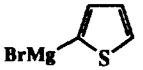
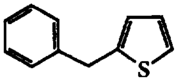
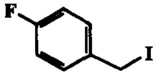
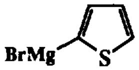
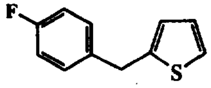
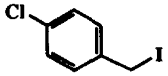
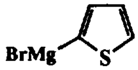
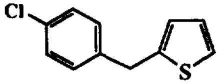
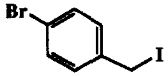
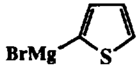
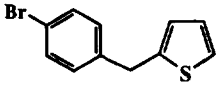
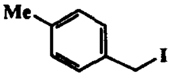
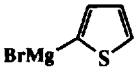
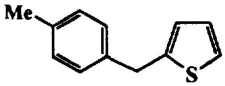
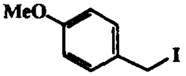
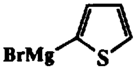
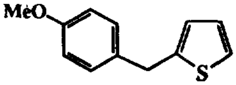
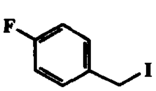
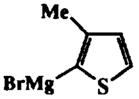
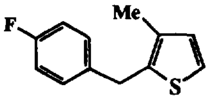
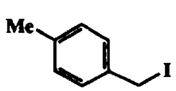
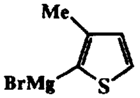
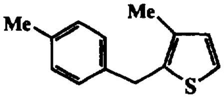
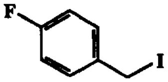
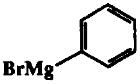
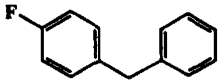
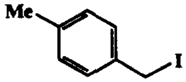
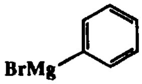
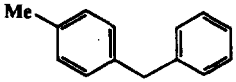
Scheme II



The reaction described in this communication exhibits many advantages over the other approaches for the synthesis of diarylmethanes. The reaction is highly efficient and high yielding. It is not only useful for the lab scale preparation of diarylmethanes, but it is also very practical for large scale production of this type of compound. For example, this reaction has been successfully used to prepare hundred kilo quantities of compound 2. This reaction minimized the formation of dimeric by-products to less than 3%.

The effectiveness of this reaction is, in part, due to the fact that the formation of the Grignard reagent from the arylhalide is easier to accomplish than the formation of benzylgrignard from benzylhalides. The later formation is often complicated by the competitive Wurtz coupling to form the dibenzyl homodimer in as much as 15%. [11]

Table I Synthesis of Diarylmethanes by Copper-Catalyzed Reaction [15]

Entry	Benzyliodides [13]	Aryl-grignards	Diarylmethanes	Yield (%)
1				92%
2				90%
3				92%
4				91%
5				90%
6				91%
7				87%
8				86%
9				84%
10				85%

* Unoptimized isolated yields. To obtain best yield, THF should be dry and free of peroxide, and the Li_2CuCl_4 solution should be freshly prepared. [14]

The copper-promoted benzyl-aryl coupling has not previously been well established. [12] Only a few arylcopper compounds have been reacted with benzyl halides to form the corresponding diarylmethanes and the yields were relatively modest (40-51%).

In summary, we have presented here a general, convenient and highly efficient synthesis of diarylmethanes *via* a copper-catalyzed reaction of arylmagnesium derivatives and benzyliodides. Various diarylmethanes can be prepared in high yield and under mild conditions by this reaction.

References and Notes

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13. Preparation of 4-fluorobenzyl iodide: A mixture of 4-fluorobenzyl chloride (14.46 g, 0.1 mol) and NaI (18.0 g, 0.12 mol) in THF (50 ml) was heated to 65°C ~ 70°C for 3 h (GC-MS showed that all the 4-fluorobenzyl chloride was converted to the 4-fluorobenzyl iodide). The mixture was cooled to room temperature and was used in the next step directly.
14. The solution was prepared by mixing lithium chloride (0.85 g, 20 mmol) and copper chloride (1.35 g, 10 mmol) in THF (100 ml) at R.T.
15. The following proceduce for preparation of 2-(4-fluorobenzyl)thiophene is representative: To a suspension of Mg (3 g, 0.123 mol) in THF (40 ml) was added a small amount of solid I_2 (20 mg). The mixture was heated to reflux under nitrogen. To the mixture was then added an aliquot of 2-bromothiophene solution (5 ml). After the iodine color disappeared, the rest of the 2-bromothiophene (total 2-bromothiophene:19.6 g, 0.12 mol, in 40 ml THF) solution was added to thesuspension dropwise, maintaining reflux. After the addition, the mixture was heated under reflux for 2 h, then was cooled to room temperature. To this mixture was added a THF solution of 4-fluorobenzyl iodide (0.1 mol) [13] followed by Li_2CuCl_4 solution (5 ml, 0.5mmol) [14] keeping the temperature under 40°C using a cool water bath. The mixture was stirred at room temperature for 2 h. To the mixture was added sat. NH_4Cl solution (100 ml), the mixture was stirred for 30 min., the organic layer was separated and washed with 10% sodium thiosulfate solution (50 ml), followed by distilled water (100 ml). The organic layer was then dried over $MgSO_4$ and concentrated to give 19 g of 2-(4-fluorobenzyl)thiophene as an oil. Purification can be achieved by vacuum distillation (110°C, 5mmHg).

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