Free catalyst Stille coupling assisted by microwaves for the synthesis of substituted diarylmethanes

Romina A. Ocampo, [ab] María G. Montiel Schneider, [ab] Andrea R. Costantino,[ab] Sandra D. Mandolesi, *[a] Liliana C. Koll*[ab]

[a] *Instituto de Química del Sur (INQUISUR), Departamento de Química, Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina.*
[b] *CONICET, Argentina.* E-mail: lckoll@criba.edu.ar; sdmando@criba.edu.ar; rocampo@uns.edu.ar.

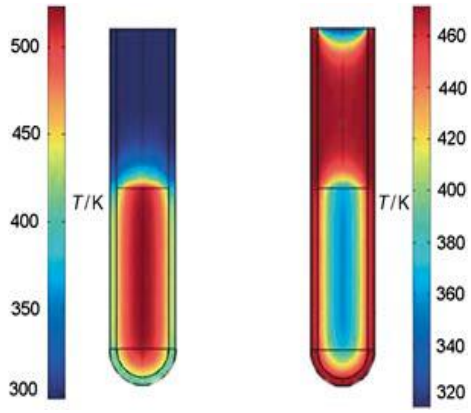
Abstract:

We present here the study of the synthesis of diarylmethanes through Stille reaction under microwave irradiation, comparing the results with and without catalytic conditions and ligands, based on the optimal results applying microwaves without catalyst that have been reported for Suzuki and Sonogashira coupling. In most cases, reactions were completed in short time and no homocoupling product was observed.

Keywords: diarylmethanes, Barbier reaction, Stille coupling, microwaves.

Introduction

Thermally driven organic transformations take place in two ways: conventional heating or microwave accelerated warming. In the first case, the reagents are slowly activated by a conventional external heat source. The heat is transferred into compounds, passing first through the balloon walls in order to achieve the solvent and reagents, so that it is a slow and inefficient method of energy transfer to the reactant system. In the second case, the microwave irradiation interacts directly with molecules of the entire reaction mixture, causing a rapid temperature increase. As the process is not conditioned by the thermal conductivity of the reaction vessel, the result is an instantaneous localized overheating of any substance that responds to rotation or dipolar ionic conduction (the two fundamental mechanisms of microwave energy transfer to the warming substance).



Since the energy transfer occurs in less than a nanosecond (10^{-9} s), the molecules are unable to completely relax (10^{-5} s) or reach equilibrium.[1] The use of microwave irradiation in organic synthesis has become a popular technique to develop and optimize the libraries of compounds synthesis in a very inferior time to those obtained with the classical thermal methods in pharmaceutical and academic production.[2] Numerous studies in the past ten years, demonstrated that microwave enhanced chemical reactions and that they are faster than conventional heating methods.[3]

Transition metals catalyzed homogeneous reactions are one of the most significant studies in the field of microwave-assisted organic synthesis. The catalyzed C-C or C-heteroatom bond formation requires fully reacting when using conventional heating under reflux conditions and always under inert atmosphere, hours and even days. In previous studies, Hallberg showed that reaction rates of many of these transformations can be significantly improved using microwave heating in closed vials without inert atmosphere.[4] The use of microwave in conjunction with metal catalysts offers significant advantages over traditional methods, since the temperature gradient reversal under microwave conditions leads to increased catalyst life through the elimination of the effect of wall.[5]

Recently, new advances in the use of organotin compounds as synthetic intermediates have been made that encouraged their preparation through faster and more convenient ways. Stille reaction was one of the earliest reactions catalyzed by transition metals accelerated by microwave heating. Single irradiation mode and short reaction times, make the microwave an attractive technique for applying Stille reactions both in solution and solid support.[6]

Results and Discussions

In previous studies, we reported the preparation of a variety of diarylmethanes obtained via ultrasound Stille coupling under palladium catalysis between some substituted aryl compounds and benzyltributyltin compounds generated through sonicated Barbier reaction in a very short time reaction and excellent yield as another contribution to the investigation of Csp^3–Csp^2 coupling process involving benzyl–aryl reagents.[7]

Continuing our studies of the synthesis of diarylmethanes, we analyzed now the Stille coupling reactions between benzyltin compounds and aryl halides under microwave activation, with and without catalyst.

In the first place, the reactions under catalyzed conditions were carried out using $Pd_2(dba)_3$/$AsPh_3$/LiCl/DMF, under 200W power irradiation at 105°C (Figure 1). The reactions were ready in less than 45 minutes (monitored by silica gel TLC).

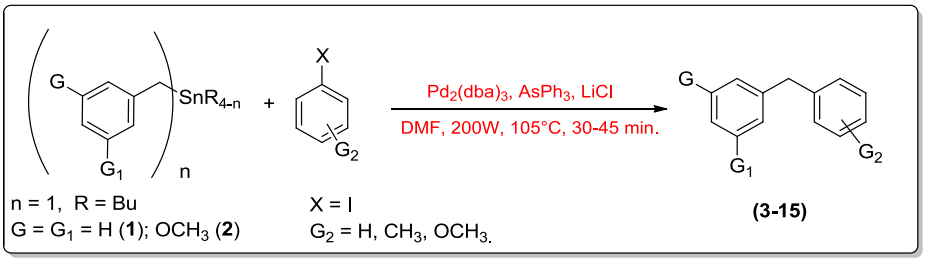
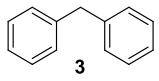
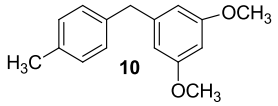
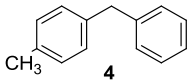
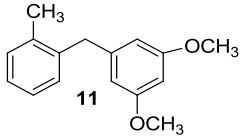
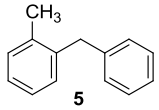
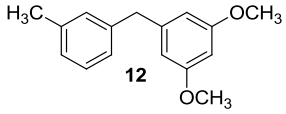
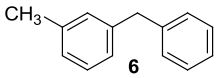
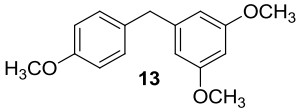
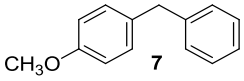
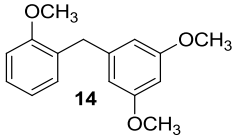
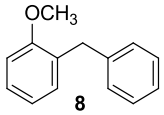
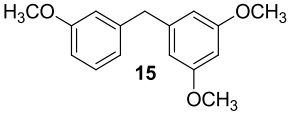
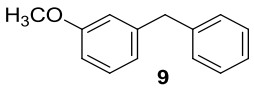


Figure 1

The results obtained are summarized in Table 1. In all cases, yields and reaction times were better than those obtained under the same conditions with sonochemical induction.[7] In addition, there was no homocoupling product formation, and the yields obtained were from moderate to very good (52-86%).

Table 1. *Catalyzed Stille coupling under microwave condition reactions.*

Entrada	Producto	Rend.[a] (%)	Tiempo (min.)	Entrada	Producto	Rend.[a] (%)	Tiempo (min.)
1	 **3**	85	30	**8**	 **10**	71	45
2	 **4**	71	40	**9**	 **11**	52	45
3	 **5**	78	40	**10**	 **12**	72	45
4	 **6**	86	40	**11**	 **13**	76	45
5	 **7**	67	40	**12**	 **14**	79	45
6	 **8**	80	40	**13**	 **15**	80	45
7	 **9**	69	45				

[a] Determined by CG-MS analysis of crude reaction through a standard curve generated from isolated pure product.

In the second place and taking into account the reported promising results in Suzuki and Sonogashira coupling reactions applying microwave without added metal catalyst,[8] we made the study of the same Stille coupling reactions but now, under *free* catalyst and ligands conditions. Since the use of metals leads to the generation of waste and can have a number of problems associated with it, the eradication of the catalyst from the Stille reaction offers significant advantages. This runs true even with today´s highly active or recyclable metal catalysts for the reaction. The preparation of these catalysts, their extraction, and product purification can be time-consuming and costly. This is of particular importance when considering the synthesis of fine chemicals such as pharmaceuticals were contamination of the product with heavy metals is highly undesirable. The effect of microwave simple application in the reaction between benzyltin substrates and different aryl halides using DMF as a solvent was analyzed, using the same conditions previously reported (300W, 150 °C, Figure 2).

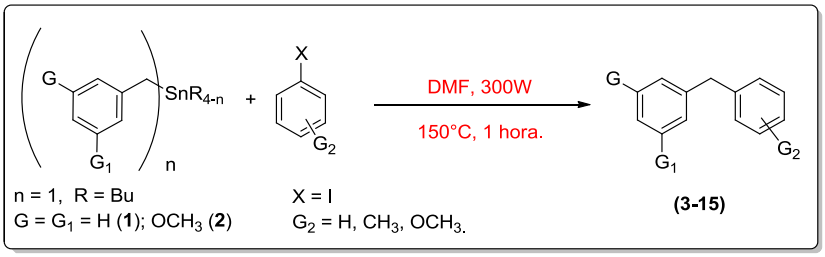
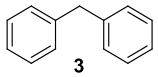
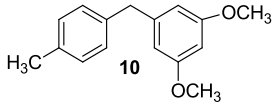
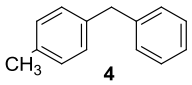
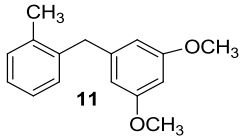
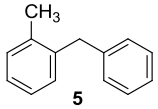
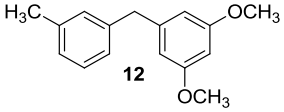
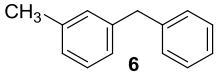
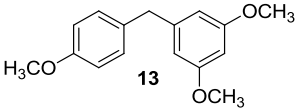
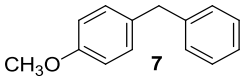
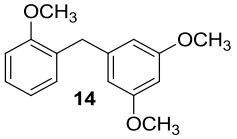
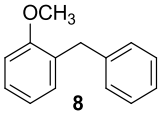
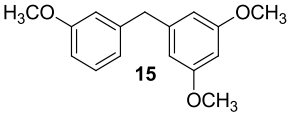
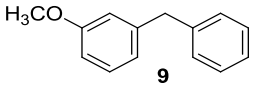


Figure 2

The results obtained after 60 min microwave irradiation are reported in Table 2. As in the case of catalyzed reactions, yields were determined by CG-MS analysis of crude reaction products.

Table 2. *Free Catalyst Stille coupling under microwave condition reactions.*

Entrada	Producto	Rend.[a] (%)	Tiempo (min.)	Entrada	Producto	Rend.[a] (%)	Tiempo (min.)
1	 3	38	60	8	 10	---[b]	60
2	 4	---[b]	60	9	 11	---[b]	60
3	 5	---[b]	60	10	 12	20	60
4	 6	35	60	11	 13	---[b]	60
5	 7	28	60	12	 14	---[b]	60
6	 8	30	60	13	 15	25	60
7	 9	---[b]	60				

[a] Determined by CG-MS analysis of crude reaction through a standard curve generated from isolated pure product. [b] No reaction observed.

Conclusions

Although reaction times are higher and the yields were lower than those found in microwave catalyzed condition, the fact that, in this case, this difficult type of reaction (Csp_3-Csp_2 coupling) can be performed without catalyst is very promising and encourages us to continue with future studies in order to find the best conditions and try to elucidate the mechanism of this C-C coupling reaction. In those cases where coupling does occur, the reaction is very clean and no homocoupling being observed.

Acknowledgments

This work was supported by grants from ANPCyT (Capital Federal, Argentina), CONICET (Buenos Aires, Argentina) and Universidad Nacional del Sur (Bahía Blanca, Argentina). A fellowship from CONICET to ARC and GMS is acknowledged.

Experimental

General methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. Dry dimethylformamide (DMF) was achieved by simple storage of the solvent over activated 3 A˚ molecular sieves. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates and visualization was accomplished with UV light and/or 5% ethanol solution of phosphomolibdic acid. Silica gel (Merck, 230-400 mesh) was used for column chromatography. Melting points were recorded on a Büchi Melting Point B-545 instrument and are uncorrected. Mass spectra were obtained with a GC/MS instrument (HP5-MS capillary column, 30 m / 0.25 mm / 0.25 mm) equipped with 5972 mass selective detector operating at 70 eV (EI). Infrared spectra were recorded with a Nicolet Nexus 470 FT spectrometer. Compounds described in the literature were characterized by comparison of their ^{1}H, and/or ^{13}C NMR and IR spectra to the previously reported data.[7]

General procedure. Synthesis of diarylmethanes (3) – (15) (microwave catalyzed Stille coupling).

All the reactions were carried out following the same procedure. One experiment is described in detail in order to illustrate the methods used.

Synthesis of 1-benzyl-3-methylbenzene (6)

A solution of benzyltri-*n*-butyltin (**1**) (0.38 g, 1 mmol), Pd_2dba_2 (2 mol%), $AsPh_3$ (30 mg, 0.012 mmol), LiCl (0.13 g, 3 mmol), 3-iodotoluene (0.22 g, 1 mmol) and DMF (4 mL) under argon atmosphere was sealed in a Pyrex tube under microwave conditions (200 mW, 105°C). After 40 min of reaction, no progress in the reaction was seen by TLC analysis. The crude product was filtered through celite to separate the inorganic insolubles salts together with the catalyst. The solvent was distilled off under reduced pressure and the crude of the reaction was analyzed by CG-MS. Product **6** was isolated by column chromatography with alumina dopped with 10% of KF to retain tributyltin halide formed during the reaction. Compound **6**

eluted with 95:5 (hexane/diethyl ether) as a yellowish oil (0.12 g, 0.68 mmol, 72%, b.p.: 276.9°C/760 mmHg, lit: b.p.: 279.2°C/760 mmHg).[9]

General procedure. Synthesis of diarylmethanes (3) – (15) (microwave free catalyst Stille coupling). Synthesis of 1-(3,5-dimethoxybenzyl)-3-methoxybenzene (15)

A solution of 3,5-dimethoxybenzyltri-*n*-butyltin (**2**) (0.44 g, 1 mmol), and 3-iodoanisole (0.22 g, 1 mmol) and DMF (4 mL) under argon atmosphere was sealed in a Pyrex tube under microwave conditions (300 mW, 150°C). After 1 h of reaction, no progress in the reaction was seen by TLC analysis. The crude product was filtered through celite to separate the inorganic insolubles salts together with the catalyst. The solvent was distilled off under reduced pressure and the crude of the reaction was analyzed by CG-MS. Product **15** was isolated by column chromatography with alumina dopped with 10% of KF to retain tributyltin halide formed during the reaction. Compound **15** eluted with 95:5 (hexane/diethyl ether) as a yellowish oil (0.065 g, 0.25 mmol, 25%).

References

1. De Pomerai, D. I.; Smith, B.; Dawe, A.; North, K.; Smith, T.; Archer, D. B.; Duce, I. R.; Jones, D.; Candido, E. P. M. *FEBS Lett.* **2003**, 543, 93.
2. (a) Hayes, B. L. *Microwave Synthesis.* **2002**. (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J.*Tetrahedron,* **2001**, 57, 9225.
3. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron,* **2001**, 57, 9225.
4. (a) M. Larhed, C. Moberg, A. Hallberg, *Acc. Chem. Res*. **2002**, 35, 717. b) K. Olofsson, M. Larhed (Eds.: P. Lidstrum, J. P. Tierney), Blackwell, Oxford, **2004**, Chapter. 2.
5. (a) J. J. Chen, S. V. Deshpande, *Tetrahedron Lett***. 2003**, 44, 8873. (b) F. Mathew, K. N. Jayaprakash, B. Fraser-Reid, J. Mathew, J. Scicinski, *Tetrahedron Lett***. 2003**, 44, 9051. (c) *J.-S. Schanche, Mol. Diversity **2003**, 7, 293. Biotage AB, www.biotage.com.*
6. (a) Larhed M., Lindeberg G., Hallberg A., *Tetrahedron Lett,* **1996,** 37, 8219. (b) Berthault A., Berteina-Raboin S., Finaru A., Guillaumet G., *QSAR Comb Sci* **2004,** 23, 850.
7. Ocampo, R.; Koll, L.; Mandolesi, S. *Ultrasonics Sonochemistry,* **2013**, 20, 40.
8. (a) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919. (b) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.
9. Lamneck, J.H.; Wise, P. H.; *J. Am. Chem. Soc.* **1954**, *76*, 1104.