Pergamon

Tetrahedron Letters 42 (2001) 175–177

TETRAHEDRON
LETTERS

# Solid-phase synthesis of diaryl ketones through a three-component Stille coupling reaction

Weiya Yun,* Shiming Li, Bingbing Wang and Li Chen

*Roche Research Center, Hoffmann-La Roche, Inc., 340 Kingsland Street, Nutley, NJ 07110, USA*

Received 7 August 2000; revised 30 October 2000; accepted 31 October 2000

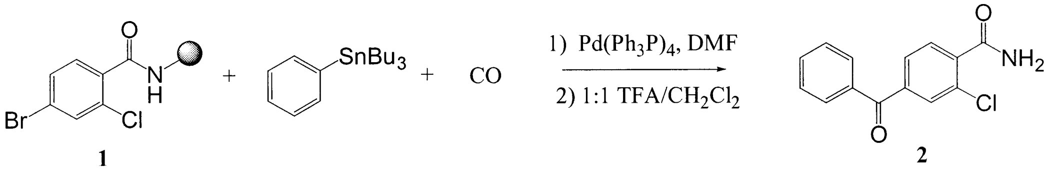
---

**Abstract**—A three-component Stille coupling reaction on solid phase is described. Diaryl ketones bearing a wide variety of functional groups were prepared with polymer-bound organostannane and aryl halides in the presence of carbon monoxide.

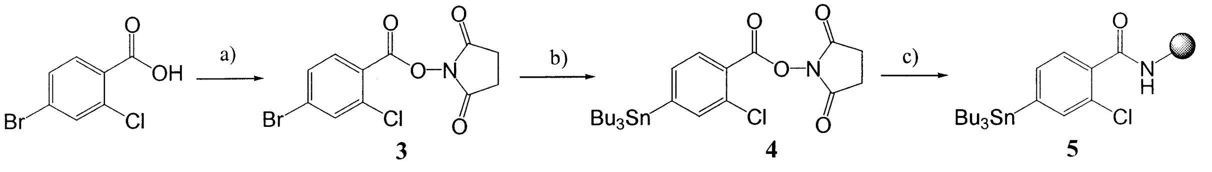
---

Diaryl ketones and their reductive products, diaryl methanes, serve as important structural scaffolds in biologically active compounds and are frequently used as bioisosteres for diaryl ethers in medicinal chemistry.[1a] Although many synthetic methods are available for the preparation of this structural component in solution phase,[1] their extension to solid-phase synthesis and chemical library production has been very limited. In 1995, Ellman and his coworkers reported the first diaryl ketone synthesis on solid support via palladium catalyzed Stille coupling reactions of resin-bound arylstannane with acid chlorides.[2] In our recent attempt for a high-throughput synthesis of diaryl ketones, we have extended this method to a three-component Stille coupling reaction on solid support in order to expand our substrate pool to aryl halides bearing polar, acid chloride sensitive substituents. Herein we wish to report our initial results on these newly developed three-component Stille coupling conditions in which a polymer-bound arylstannane was coupled with aryl halides in presence of carbon monoxide.

To demonstrate the feasibility of this reaction on solid-phase support, Rink resin (1% cross linked, 0.54 mmol/g) bound aryl bromide **1** was first reacted with tributylphenyltin in the presence of carbon monoxide and $Pd(Ph_3P)_4$ in DMF (Scheme 1).[3] It was found that the coupling reaction took place selectively at the



**Scheme 1.** Three-component Stille coupling reaction on solid-phase support.



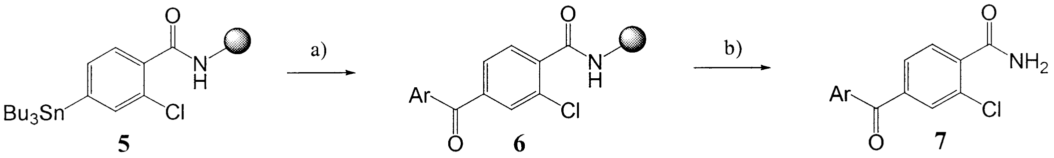
**Scheme 2.** (a) *N*-Hydroxysuccinimide; EDCI, DMF, 23°C, 16 h, 92% yield; (b) $(Bu_3Sn)_2$, $Pd(Ph_3P)_4$, toluene, reflux, 15 h;[5] (c) Rink amide resin, DMF, 23°C, 16 h.

---

*Keywords*: solid-phase synthesis; Stille coupling; diaryl ketone.

* Corresponding author. Tel.: (973) 235-3126; fax: (973) 235-6084; e-mail: weiya.yun@roche.com

0040-4039/01/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)01937-7



5 6 7

**Scheme 3.** (a) ArX, $Pd(Ph_3P)_4$, CO, 40 psi, DMSO, 80°C, 18 h if X = I, 3 days if X = Br; (b) 1:1 $TFA/CH_2Cl_2$, 23°C, 0.5 h.

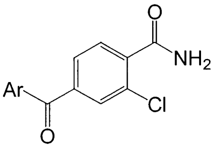
bromine position and finished within 6 h at 80°C under 40 psi of carbon monoxide. Upon cleavage from the polymer with TFA, aryl ketone **2** was obtained in quantitative yield with high purity (>95%).[4] Further investigation of reaction conditions revealed that both DMF and DMSO provided satisfactory results, and $Pd(Ph_3P)_4$ appeared to be a better catalyst than $Pd_2(dba)_3$. Carbon monoxide pressure of 40–60 psi appeared to be required for high conversion.

The success of this reaction prompted us to explore the reversed three-component Stille coupling on solid support with arylstannane as an immobilized component and the more readily available aryl halides as building blocks.

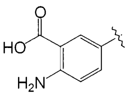
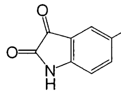
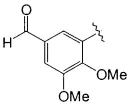
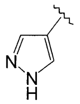
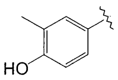
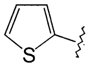
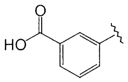
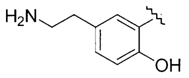
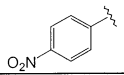
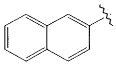
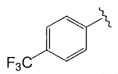
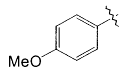
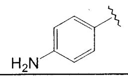
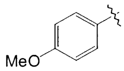
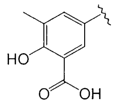
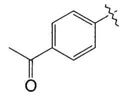
Preparation of the polymer-bound stannane component **5** is shown in Scheme 2. 4-Bromo-2-chloro benzoic acid was first converted to *N*-hydroxysuccinimide ester **3** via carbodiimide promoted coupling. The bromine at the para position of the activated ester was then reacted with bis(tributyltin) in presence of a catalytic amount of $Pd(Ph_3P)_4$ in anhydrous toluene at 140°C to afford the arylstannyl ester **4**.[5] Direct reaction of the resulting **4** with Rink amide resin at 23°C in DMF for 16 h afforded **5**, and the loading was determined to be quantitative.

The three-component reversed Stille coupling reaction on the polymer (Scheme 3) was carried out under similar reaction conditions as described in Scheme 1.

**Table 1.** Structure of diaryl ketone prepared through a three-component Stille coupling reaction



7

| Entry | Ar[a] | Product Purity (Yield)[4] | Entry | Ar[a] | Product Purity (Yield)[4] |
|---|---|---|---|---|---|
| 7a |  | 86 (81) | 7i |  | 92 (99) |
| 7b |  | 98 (92) | 7j |  | 93 (93) |
| 7c |  | 98 (90) | 7k |  | 100 (99) |
| 7d |  | 98 (94) | 7l |  | 94 (88)[b] |
| 7e |  | 78 (89) | 7m |  | 97 (38) |
| 7f |  | 99 (93) | 7n |  | 97 (98) |
| 7g |  | 90 (99) | 7o |  | 17 (94)[c] |
| 7h |  | 96 (90) | 7p |  | 21 (95)[c] |

[a] Entries **7a**–**l** were prepared from ArI, **7m** and **7n** from ArBr, **7o** and **7p** from ArOTf. [b] Made from 3-iodo-L-tyrosine; the isolated product was decarboxylated. [c] Product contains 2-chlorobenzamide due to partial reduction of **5**.

The reactions were performed in pressure tubes arranged in a heating block on a shaker. In our case sixteen reactions were run simultaneously. Upon cleavage from the resin, ketone **7** was obtained in good to excellent yields and purity (Table 1).[6] As expected, different halide classes exhibited different reactivities toward the organotin reagent. While chlorine is totally inert under these reaction conditions, aryl bromides and aryl iodides showed acceptable to excellent reactivities toward **5** despite the fact that the stannane component is deactivated by the para amide group. The majority of reactions with aryl iodides finished within 6 h, although all reactions were heated at 80°C for 18 h to ensure complete conversions. In the case of aryl bromides, three to four days were required. Like the solution phase reactions previously reported,[3,7] the presence of LiCl showed no effect with aryl halides, while it indeed enhanced the reaction rate for aryl triflates. In contrast, unlike the reactions in solution phase, aryl triflates, under these conditions, are less reactive than aryl bromides. Although pure products were generated in the presence of LiCl, none of the reactions could be completed in four days. In all cases, diaryl ketones were the sole products, and no direct cross coupling products were observed.

The great functional group tolerance of this three-component Stille coupling reaction has substantially increased our substrate building block pool. Not only can the aryl halides containing methoxy (**7b** and **7n**), nitro (**7e**), trifluoromethyl (**7f**) and hetero cyclic substituents (**7j** and **7k**) react smoothly with resin bound **5** to give the desired diaryl ketone products, those containing carboxylic acid (**7a**, **7d**, and **7h**), aniline (**7a** and **7g**), aldehyde (**7b**), ketone (**7i** and **7p**), phenol (**7c**, **7h** and **7l**) and even amine (**7l**) can also be directly coupled to resin **5** without protection. The electronic effect of the substituents in aryl halides to the coupling reaction was not manifested under the aforementioned conditions since both electron-donating groups (**7c**, **7g** and **7n**) and electron withdrawing groups (**7d**–**f**) containing aryl halides afforded diaryl ketones in similar yield and purity.

In conclusion, we have successfully implemented a three-component Stille coupling reaction on solid support. Diaryl ketones with a wide range of functional groups were synthesized directly without tedious protection and deprotection steps. This diaryl ketone synthesis constitutes a complementary approach to the synthesis via acid chlorides and may find broad application in high throughput synthesis and lead optimization process in medicinal chemistry. An application of this synthesis to ketone library production along with SAR results will be reported in due course.

## Acknowledgements

The authors wish to acknowledge Mr. P. P. Riggio, Ms. M. Jonca and Mr. G. J. Sasso for sample analysis.

## References

1. (a) Taber, D. F.; Sethuraman, M. R. *J. Org. Chem.* **2000**, *65*, 254 and references cited in; (b) Brunet, J. J.; Chauvin, R. *Chem. Soc. Rev.* **1995**, *24*, 89.
2. (a) Plunkett, M. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306; (b) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006.
3. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508; (b) Scott, W. J.; Crisp, G. T.; Stille, J. K. *Org. Synth.* **1990**, *68*, 116; (c) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
4. The isolated yield was calculated based on Rink amide resin substitution level. The purity was determined based on area of peak corresponding to the correct molecular weight by a C18 reverse phase HPLC column (Chromegabond WR-C18, $3\mu$, 10–90% $CH_3CN/H_2O$ containing 0.02% TFA), monitored by UV detection at 215 nm and by a SEDEX 55 evaporative light scattering detector (ELSD). The purity scores reported herein are based on ELSD.
5. (a) Ohmomo, Y.; Murakami, K.; Hirata, M.; Magata, Y.; Tanaka, C.; Yokoyama, A. *Chem. Pharm. Bull.* **1994**, *42*, 913; (b) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49.
6. The general procedure for the solid-phase three-component Stille coupling is as follows. Resin **5** (100 mg), an aryl iodide (5 equiv.) or an aryl bromide (10 equiv.), and $Pd(Ph_3P)_4$ (0.02 equiv.) were suspended in DMSO (3 ml) in a pressure tube (ACE catalog #: 8648-135 for the tube; 5844-76 for the Teflon adapter). The tube was capped and connected onto a three-way valve with a carbon monoxide tank and a vacuum source already connected (Swagelok catalog #: SS-QC4-B-400 and SS-QC4-D-4PM). The tube was charged with CO to 40 psi and was then evacuated. The purging procedure was repeated four times and the tube was finally charged with 40 psi of CO. The sealed tube was heated to 80°C for 18 h in a heating block on a shaker. After cooling to ambient temperature, the pressure in the tube was released and the reaction mixture was transferred to a filtration tube equipped with a frit at the bottom. The resin was filtered, washed repeatedly with $CH_2Cl_2$ and MeOH, and dried under vacuum. The diaryl ketone generated was then cleaved from the resin with 1:1 $TFA/CH_2Cl_2$ at 23°C for 0.5 h. All diaryl ketones showed satisfactory spectroscopic and analytical data. NMR data for **7k**: $^1H$ NMR (400 MHz, DMSO) $\delta$ 8.18 (dd, 1H, $J=4.8$, 0.8 Hz), 8.05 (br s, 1H), 7.85 (d, 1H, $J=1.6$ Hz), 7.81 (dd, 1H, $J=8.0$, 2.0 Hz), 7.78 (br s, 1H), 7.74 (dd, 1H, $J=4.0$, 1.2 Hz), 7.61 (d, 1H, $J=8.0$ Hz), 7.32 (dd, 1H, $J=5.2$, 4.0 Hz); $^{13}C$ NMR (100 MHz, DMSO) $\delta$ 185.5, 167.4, 145.0, 140.3, 139.2, 136.6, 136.1, 130.0, 129.5, 129.1, 128.8, 127.4; IR (neat) $\nu_{max}$ 3432, 3330, 3097, 1688, 1654, 1624, 1549, 1512, 1485, 1411, 1353, 1294 $cm^{-1}$.
7. (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557; (b) Sieber, F.; Wentworth Jr., P.; Janda, K. D. *J. Comb. Chem.* **1999**, *1*, 540.