

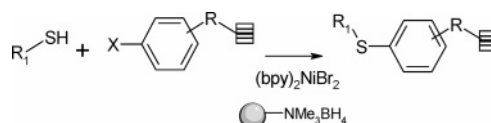
Solid-Phase Synthesis of Diaryl Sulfides: Direct Coupling of Solid-Supported Aryl Halides with Thiols Using an Insoluble Polymer-Supported Reagent

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ABSTRACT



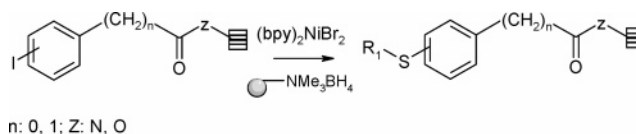
Diaryl sulfides have been prepared by direct nickel(II)-catalyzed coupling of thiols with iodoaryl bound to SynPhase polystyrene lanterns in the presence of polymer-supported borohydride.

The solid-phase synthesis of nonpeptide compounds has become a standard tool of the drug discovery process.¹ On the other hand, the use of insoluble polymer-bound reagents for organic synthesis has increased in the past few years.²

Metal-catalyzed synthesis of aryl sulfides is of current interest. Efficient copper- or palladium-catalyzed C–S bond formations under mild conditions have been described.³ Recently, we reported a very useful method for coupling selenolates as well as thiolates with aryl halides in solution phase using polymer-supported borohydride.⁴

In the course of our parallel synthesis programs, we sought to apply this methodology for coupling a large number of

Scheme 1. Nickel-Catalyzed Carbon–Sulfur Formation



n: 0, 1; Z: N, O

commercially available thiols with aryl halides grafted on polystyrene SynPhase lanterns⁵ using the mix and sort approach.

We report here, the first application, to the best of our knowledge, using a mixture of supported reactant and supported reagent. We have investigated the scope and limitation of this new preparative method for obtaining a small library of diaryl sulfides by reacting commercially available thiols with aryl or heteroaryl halides bound to HMP or RAM polystyrene SynPhase lanterns in the presence of IRA 400 borohydride resin⁶ using nickel bipyridine dibromide as a catalyst⁷ (Scheme 1).

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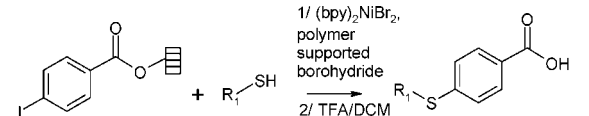
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Table 1. Nickel-Catalyzed Coupling of 4-Iodobenzoic Acid Supported on SPPSLHMP Lanterns

				
Entry	R ₁ SH	Product	Purity ^a (%)	Yield ^b (%)
1			96	100
2			95	100
3			95	100
4			96	100
5			92	100
6			60	100

^a Crude purity based on HPLC.⁹ ^b Isolated yield for recovered material based on initial loading.

Commercially available SPPSLHMP lanterns were coupled with iodobenzoic acids using DIC as the coupling reagent of choice in the presence of a catalytic amount of DMAP.⁸

The resulting iodoaryl compounds were coupled with a series of thiols.¹⁰ Usually, reactions with SynPhase lanterns take place without stirring. However, because of the presence of the borohydride-supported reagent, efficient stirring is required. The two insoluble polymer-supported species were kept separate in the reactor by means of porous gauze. After cleavage from the lanterns, final products were isolated without purification.

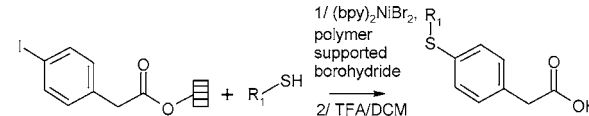
The coupling of some thiols with 4-iodobenzoic acid bound to HMP lanterns was examined first (Table 1). Substituted phenyl thiols were efficiently coupled to provide the corresponding diaryl sulfide products in excellent purity. The presence of electron-donating groups (entries 1 and 3), ortho substitution (entries 2 and 4), or electron-withdrawing groups (entries 5) has almost no influence on the coupling reaction. The use of heterocyclic thiols carrying bulky groups (entry 6) gave lower purity compared to the phenyl thiols in entries 1–5. Under our cleavage conditions, the product in entry 6 was obtained as the corresponding ammonium trifluoroacetate.

(8) For a typical procedure for coupling a carboxylic acid with SPPSL-HMP lanterns, see Supporting Information.

(9) For details concerning the LC/MS analyses, see Supporting Information.

(10) For a typical procedure for coupling reaction of thiols, see Supporting Information.

Table 2. Nickel-Catalyzed Coupling of 4-Iodophenyl Acetic Acid Supported on SPPSLHMP Lanterns

				
Entry	R ₁ SH	Product	Purity ^a (%)	Yield ^b (%)
7			80	94
8			75	70
9			90	91
10			69	100
11			96	94
12			86	99

^a Crude purity based on HPLC.⁹ ^b Isolated yield for recovered material based on initial loading.

We then turned our attention to evaluating the reactivity of various aryl iodides under these reaction conditions. Although there is a slight decrease in the purity with thiols bearing electron-donating substituents (entries 7–10, Table 2), compared with iodobenzoic acid, the iodophenyl acetic acid afforded the desired diaryl sulfides in good yields.

Diaryl sulfide (entry 10) was obtained as a mixture of the desired product (69%) and the corresponding sulfoxide (22%). Although an oxidation reaction occurred during cleavage, the coupling step worked well. Steric hindrance on the iodoaryl acid does not appear to pose a major problem, as 4-iodo-3-methyl benzoic acid gave results comparable to 4-iodobenzoic acid (Table 3). Thiophenol bearing a *para*-trifluoromethyl (entry 17) or methoxy group (entry 15) can be coupled in good yield. This demonstrates that the protocol can be applied equally to electron-rich and -deficient thiols.

When the iodine atom was moved from the *para* to the *meta* position relative to the carboxylic acid (Table 4), the purities remained satisfactory but were inferior to those obtained for the *para*-iodobenzoic acids (entries 19–23). The triazole thiol afforded the desired product with a low purity (entry 23). A combination of steric hindrance and a loss of electronic activation of the iodide caused by the presence of the carbonyl functionality resulted in a slight decrease in reactivity.

We then investigated the influence of various linkers on the efficiency of the coupling reaction. When iodobenzoic

Table 3. Nickel-Catalyzed Coupling of 4-Iodo-3-methylbenzoic Acid Supported on SPPSLHMP Lanterns

Entry	R ₁ SH	Product	Purity ^a (%)	Yield ^b (%)
13			87	100
14			93	100
15			93	100
16			71	100
17			92	100
18			76	100

^a Crude purity based on HPLC.⁹ ^b Isolated yield for recovered material based on initial loading.

acids were grafted onto RAM lanterns,¹¹ the products in entries 24–28 were obtained in good yields and purity (Table 5). As expected, replacement of the ester by an amide has almost no influence on the coupling reaction. With some less reactive species such as *para*-iodophenol or *para*-iodobenzyl alcohol grafted onto HMP lanterns,¹² the purity decreased with thiols bearing electron-donating groups (entries 29 and 31, Table 6) and was good when the arylthiol was activated by an electron-withdrawing group (entries 30 and 32). With some less reactive species such as *para*-iodophenol or *para*-iodobenzyl alcohol grafted onto HMP lanterns, products in entries 29–32 were obtained in moderate yields (20–30%).

We then attempted to improve the coupling rate of the iodobenzoic acid derivatives by increasing the reaction temperature and thiol concentration (Table 7). Ethyl alcohol was replaced with *n*-butanol, and the temperature was slightly

(11) For a typical procedure for coupling a carboxylic acid with SPPSLRAM lanterns, see Supporting Information.

(12) For a typical procedure for coupling an alcohol with SPPSLHMP (0.16 μmol) SynPhase lanterns, see Supporting Information.

(13) **Typical Procedure for Coupling Reaction of Thiols.** A mixture of thiol (0.5 M), (bpy)₂NiBr₂ (0.05 equiv), and borohydride polymer-supported Amberlite IRA400 (2.5 mmol/g) (0.5 M) and SynPhase lanterns in ⁿBuOH/THF (1 mL per lantern) was stirred at 100 °C for 15 h in a reactor fitted with a polypropylene gauze to avoid contact between SynPhase lanterns and resin. SynPhase lanterns were washed with THF (three times with 5 mL per lantern), EtOH (5 mL per lantern), and DCM (three times with 5 mL per lantern).

Table 4. Nickel-Catalyzed Coupling of 3-Iodo-4-iodobenzoic Acid Supported on SPPSLHMP Lanterns

Entry	R ₁ SH	Product	Purity ^a (%)	Yield ^b (%)
19			75	100
20			92	100
21			89	100
22			89	100
23			50	100

^a Crude purity based on HPLC.⁹ ^b Isolated yield for recovered material based on initial loading.

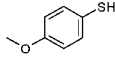

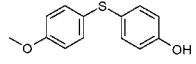
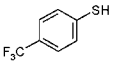

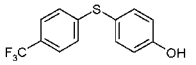
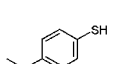
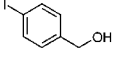
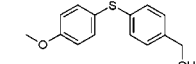
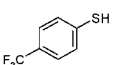
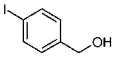
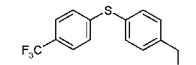
Table 5. Nickel-Catalyzed Coupling of 4-Iodobenzamide Supported on SPPSRAM Lanterns

Entry	R ₁ SH	Product	Purity ^a (%)	Yield ^b (%)
24			93	100
25			97	100
26			96	100
27			95	100
28			94	100

^a Crude purity based on HPLC.⁹ ^b Isolated yield for recovered material based on initial loading.

increased from 70 to 100 °C.¹³ The rate of conversion increased considerably, as the desired products were obtained in good purity compared with entries 6 and 23 and good yields (70 and 80%).

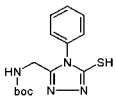
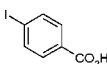
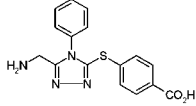
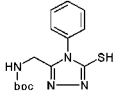
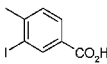
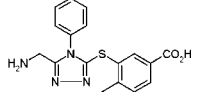
Table 6. Nickel-Catalyzed Coupling of 4-Iodoaryl Alcohol Acid Supported on SPPSLHMP Lanterns

$ \begin{array}{c} \text{I} \\ \\ \text{C}_6\text{H}_4\text{---}(\text{CH}_2)_n\text{---O---} \text{[Polymer Support]} \\ + \text{R}_1\text{---SH} \xrightarrow[\text{2/ TFA/DCM}]{\text{1/ (bpy)}_2\text{NiBr}_2, \text{ polymer supported borohydride}} \text{R}_1\text{---S---C}_6\text{H}_4\text{---}(\text{CH}_2)_n\text{---OH} \end{array} $				
Entry	R ₁ SH	Ar-I	Product	Purity ^a (%)
29				60
30				89
31				46
32				86

^a Crude purity based on HPLC.⁹

This investigation has demonstrated the general applicability of the mixed supported reactant/supported reagent method of synthesis. As a part of this work, we successfully developed the nickel-catalyzed coupling reaction of arylthiols with supported iodoaryl compounds. Because a large number of thiols, iodoaryl acids, and iodoaryl alcohols are commercially available, the versatility of this new protocol

Table 7. Effect of Temperature on the Coupling Rate

$ \begin{array}{c} \text{I} \\ \\ \text{C}_6\text{H}_4\text{---COO---} \text{[Polymer Support]} \\ + \text{R}_1\text{---SH} \xrightarrow[\text{2/ TFA/DCM}]{\text{1/ (bpy)}_2\text{NiBr}_2, \text{ polymer supported borohydride}} \text{R}_1\text{---S---C}_6\text{H}_4\text{---COOH} \end{array} $				
Entry	R ₁ SH	Ar-I	Product	Purity ^a (%)
33				97
34				96

^a Crude purity based on HPLC.⁹

allowed the synthesis of a diversified library of diaryl sulfides.

Acknowledgment. Drs. G. Laffet and M. Aurelly are acknowledged for providing analysis for all compounds.

Supporting Information Available: HPLC/MS, NMR (¹H, ¹³C), and HRMS of all compounds and experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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