



## A copper-free, cross-coupling of terminal alkynes with hetaryl halides



Pavel Arsenyan\*, Kira Rubina, Jelena Vasiljeva, Sergey Belyakov

Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006 Riga, Latvia

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### ABSTRACT

Substituted ethynyl heterocycles and heteroarylbutenyne are synthesized efficiently in good yields via a copper-free, cross-coupling reaction.

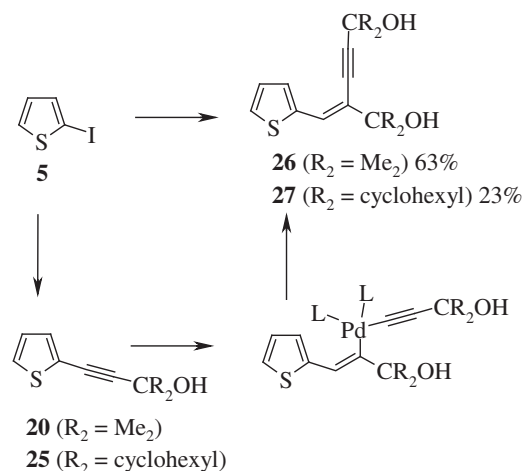
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The elaboration of novel eco-friendly methods in synthetic organic chemistry has gained significant attention. Procedures using heterogeneous conditions for transition metal catalyzed cross-coupling reactions under 'green chemistry' protocols are of interest.<sup>1</sup> In fact, palladium on charcoal is a very popular catalyst for the formation of C–C bonds in Suzuki–Miyaura, Heck, and Sonogashira reactions. Recently, Lipshutz and co-workers reported the synthesis of a new active palladium on charcoal species and its use as a catalyst for Sonogashira couplings.<sup>2a</sup> The Pham-Huu group<sup>2b</sup> has published microwave-promoted alkylation reactions of aryl bromides with palladium-loaded multi-walled carbon nanotubes.

Motivated by the importance of developing direct and facile methods for the synthesis of substituted ethynyl heterocycles using commercially available, eco-friendly, and inexpensive reagents, we examined the copper-free cross-coupling reaction of terminal alkynes with hetaryl halides.

In the first step of our investigation, we performed preliminary optimization of the reaction conditions. Ethanol was chosen as the solvent due to its being more eco-friendly in comparison to other alcohols (isopropanol, propanol, and methanol). In our experiments we used regular ethanol (not dried) containing up to 4% water. The main purpose of the study was to use a heterogeneous palladium catalyst and a cheap phosphine ligand at the lowest, but optimal concentration. *N*-Benzyl-3-iodopyrazole (**1**) and phenylacetylene were chosen as model compounds for the optimization.<sup>3</sup>

According to our experimental data, the use of only 1% of palladium on charcoal and 2% of triphenylphosphine in the presence of three equivalents of potassium carbonate led to the formation of the desired product, *N*-benzyl-3-(phenylethynyl)pyrazole (**8**)<sup>3a</sup> in almost quantitative yield (98%). Utilization of a lower amount of catalyst reduced the total yield of **8**. After completion of the reaction in ethanol, the solution was filtered through a short pad of silica gel to remove the catalyst and then evaporated. It should be noted that according to GC–MS, no triphenylphosphine or its phosphorane was present in solution. The absence of unabsorbed

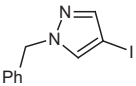
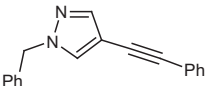
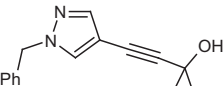
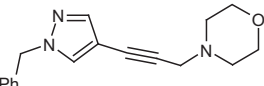

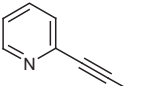
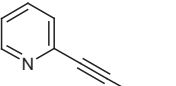
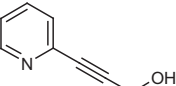
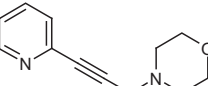

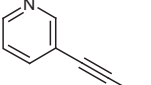
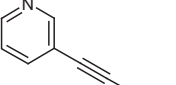
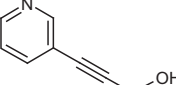

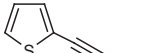
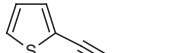
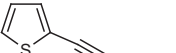
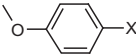
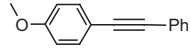
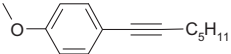
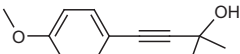



Scheme 1. Cross-coupling of terminal alkynes with 2-iodothiophene.

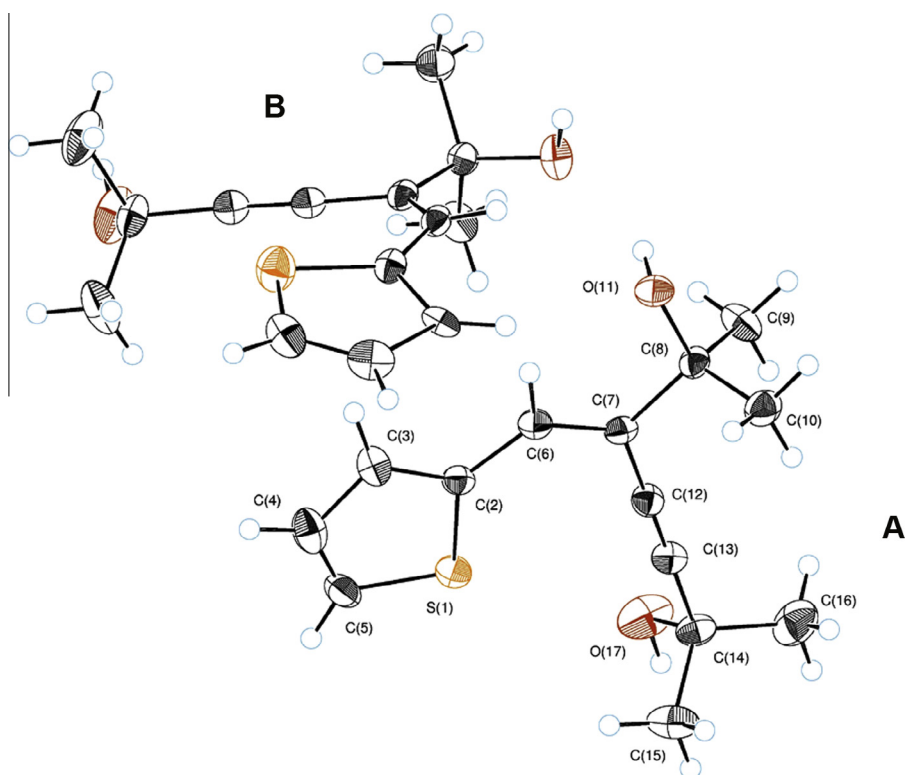
\* Corresponding author.

E-mail address: [pavel.arsenyan@lycos.com](mailto:pavel.arsenyan@lycos.com) (P. Arsenyan).

**Table 1**  
Copper-free cross-coupling of terminal alkynes with hetaryl halides

Hetaryl halide	R=			
	Ph	C <sub>5</sub> H <sub>11</sub>	CMe <sub>2</sub> OH	CH <sub>2</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O
 <b>1</b>	 <b>8</b> , <sup>3a</sup> 98%	Trace	 <b>17</b> , <sup>3b</sup> 68%	 <b>22</b> , <sup>3c</sup> 60%
 <b>2</b>	 <b>9</b> , 98%	 <b>13</b> , <sup>3d</sup> 77%	 <b>18</b> , <sup>3f</sup> 67%	 <b>23</b> , <sup>3g</sup> 79%
 <b>3</b>	 <b>10</b> , 97%	 <b>14</b> , <sup>3e</sup> 85%	 <b>19</b> , <sup>3f</sup> 73%	Trace
 <b>4</b> X=Br, <b>5</b> X=I	 <b>11</b> , <sup>3h</sup> X=Br (78%); X=I (89%)	 <b>15</b> , <sup>3i</sup> X=Br (59%); X=I (91%)	 <b>20</b> , <sup>3j</sup> X=Br (72%); X=I (46%)	Trace
 <b>6</b> X=Br, <b>7</b> X=I	 <b>12</b> , <sup>3n</sup> X=Br (88%); X=I (64%)	 <b>16</b> , <sup>3o</sup> X=Br (96%); X=I (59%)	 <b>21</b> , <sup>3p</sup> X=Br (95%); X=I (74%)	 <b>24</b> , <sup>3q</sup> X=Br (40%); X=I (71%)

Conditions: hetaryl halide (1.0 mmol), terminal acetylene (1.2 mmol), K<sub>2</sub>CO<sub>3</sub> (4.0 mmol), PPh<sub>3</sub> (0.02 mmol), 10% palladium on charcoal (0.01 mmol) in EtOH (10 ml).



**Figure 1.** ORTEP representation of the structure of compound **26**.

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