Synthesis of Aromatic Heterocycles via Palladium-Catalyzed Annulation of Internal Alkynes

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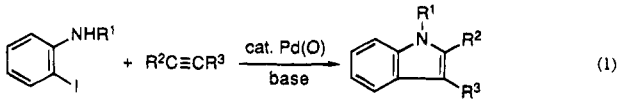
The transition-metal mediated cycloaddition reactions of alkynes are of great current interest.[1] While palladium is among the most widely studied metals for such processes,[2] multiple alkyne insertions, or insertion and subsequent cyclization back on to a preexisting aromatic ring, usually predominates. Recent success in the synthesis of indoles by the regioselective, palladium-catalyzed heteroannulation of internal alkynes (eq 1)[3] encouraged us to apply this methodology to the synthesis



(1)

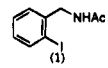
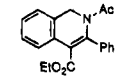
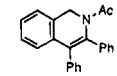
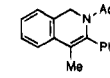
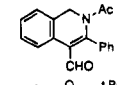
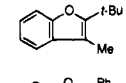
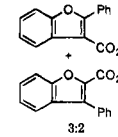
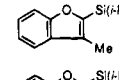
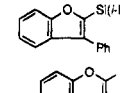
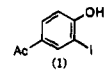
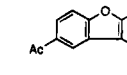
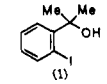
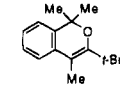
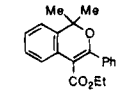
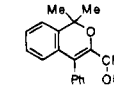
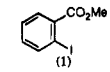
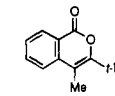
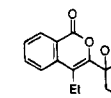
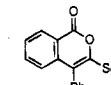
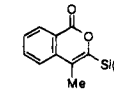
of other heterocycles. We now report that this chemistry provides a valuable new route to a wide variety of heterocycles, including 1,2-dihydroisoquinolines, benzofurans, benzopyrans, and isocoumarins. Our preliminary results are summarized in Table 1.

In general, we have employed reaction conditions similar to those reported earlier by us for the annulation of alkynes,[3a] vinylic cyclopropanes and cyclobutanes,[4] allenes,[5] and 1,3-dienes.[6] Five molar percent $Pd(OAc)_2$, sodium or potassium acetate or carbonate, LiCl or *n*-Bu_4NCl, and occasionally five molar percent PPh_3, in DMF as solvent generally gives the best results. Temperatures of 80–140 °C are necessary to effect annulation in reasonable reaction times.

We initiated our studies using *o*-iodobenzylamine, but annulation with this substrate proved sluggish and even at elevated temperatures only low yields of 1,2-dihydroisoquinolines could be obtained. By employing the corresponding acetamide, instead of the free amine, we were able to obtain vastly improved results (entries 1–4).[7] Alkynes containing aryl or carbonyl-containing groups generally gave the best results and proved highly regioselective.

We next turned to oxygen nucleophiles. Heteroannulation using *o*-iodophenol proved more difficult than analogous reactions of *o*-iodoaniline (entries 5–8). Generally, higher temperatures are required and the process appears limited to hindered alkyl acetylenes or acetylenes bearing aryl, carbonyl, or silyl groups. At the higher temperatures required, reduced regioselectivity is sometimes observed. For example, the annulation of ethyl phenylpropiolate (entry 6) at 135 °C afforded a 3:2

Table 1. Palladium-Catalyzed Heteroannulation of Alkynes[a]

entry	aryl iodide (equiv)	alkyne (equiv)	chloride source, base (equiv), PPh_3, temp (°C), time (h)	product(s)	% isolated yield
1	 (1)	PhC≡CCO$_2$Et (2)	LiCl, KOAc (2), –, 100, 24		80
2	(1)	PhC≡CPh (2)	*n*-Bu_4NCl, KOAc (2), –, 120, 24		83
3	(1)	PhC≡CMe (2)	*n*-Bu_4NCl, Na_2CO_3 (2), +, 100, 48		62
4	(1)	PhC≡CCHO (2)	LiCl, NaOAc (2), –, 100, 24		56
5	 (1)	*t*-BuC≡CMe (5)	*n*-Bu_4NCl, Na_2CO_3 (5), +, 100, 24		66
6	(1)	PhC≡CCO$_2$Et (1.1)	LiCl, K_2CO_3 (5), +, 135, 24	 3:2	69[b]
7	(1.5)	MeC≡CSi(*i*-Pr)$_3$ (1)	LiCl, Na_2CO_3 (1), –, 100, 72		90
8	(2.8)	PhC≡CSi(*i*-Pr)$_3$ (1)	LiCl, Na_2CO_3 (1), –, 100, 504		70
9	 (1)	*t*-BuC≡CMe (5)	*n*-Bu_4NCl, KOAc (5), +, 100, 24		75
10	 (1)	*t*-BuC≡CMe (2)	LiCl, Na_2CO_3 (2), –, 100, 20		52
11	(1)	PhC≡CCO$_2$Et (2)	LiCl, Na_2CO_3 (2), –, 80, 8		61
12	(1)	PhC≡CCMe$_2$(OH) (2)	LiCl, Na_2CO_3 (2), –, 100, 15		57
13	 (1)	*t*-BuC≡CMe (2)	LiCl, Na_2CO_3 (1), –, 100, 24		72
14	(1)	(2)	LiCl, Na_2CO_3 (1), –, 100, 48		63
15	(1)	PhC≡CSiMe$_3$ (2)	LiCl, Na_2CO_3 (1), –, 100, 84		63[c]
16	(1)	MeC≡CSi(*i*-Pr)$_3$ (2)	LiCl, Na_2CO_3 (1), –, 100, 24		76

[a] Entries 1-5 were run on a 0.25 mmol scale and entries 6-16 on a 0.50 mmol scale. A representative procedure for the 0.5 mmol scale follows: 5 mol % $Pd(OAc)_2$, aryl iodide (0.5 mmol), *n*-Bu_4NCl or LiCl (0.5 mmol), base (0.5, 1.0 or 2.5 mmol), DMF (10 ml), and where necessary 5 mol % PPh_3, were placed in a 4 dram vial and heated at the appropriate temperature for the indicated time. [b] Dimethylacetamide (20 ml) was used as the solvent. [c] Acetonitrile (10 ml) was used as the solvent.

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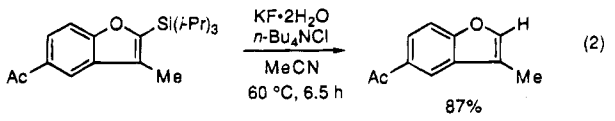
mixture of regioisomers. Hindered silylalkynes give high yields of the corresponding 2-silylbenzofurans (entries 7 and 8). This process nicely complements the palladium-catalyzed coupling of *o*-iodophenol and terminal alkynes, which affords 2-substituted benzofurans,[8,9] because the silyl-substituted benzofurans are readily desilylated to 3-substituted benzofurans by fluoride salts (eq 2).



(2)

Although alcohols are not particularly good nucleophiles in palladium-based methodology, *o*-iodobenzylic alcohols have proven effective for the synthesis of benzopyrans (entries 10–12), best results again being obtained using hindered alkyl, aryl, or carbonyl-containing alkynes.

We have also examined the annulation of internal alkynes by *o*-iodobenzoic acid and derivatives. The acid itself gives only low yields of isocoumarins and many side products. Heck et al. have shown previously that diphenylacetylene could be annulated by methyl *o*-iodobenzoate, although the analogous reaction of 3-hexyne gave very poor results.[10,11] Under our conditions, we have been able to achieve good yields of isocoumarins from methyl *o*-iodobenzoate and hindered alkyl-, silyl-, or aryl-substituted internal alkynes (entries 13–16). With certain silylalkynes, cleaner reactions could be obtained using acetonitrile as the solvent (entry 15), although longer reaction times were required.

The regiochemistry of this process follows the pattern established in our indole synthesis[3] and prior alkyne addition chemistry[2] in which the aryl group adds to the less hindered end of the alkyne and the palladium moiety to the more hindered end. The regiochemistry of the insertion of PhC≡CCO_2Et,[12] PhC≡CCHO,[12a] and *t*-BuC≡CMe[3] is based on analogous chemistry reported earlier. Desilylation of the silylbenzofuran shown in eq 2 (formed in 62% yield) afforded a benzofuran whose ^{1}H NMR spectrum was consistent with the assigned structure. The silylisocoumarins of entries 15 and 16 were desilylated to known compounds.[13] While the regioselectivity is usually excellent, successful annulation generally requires the presence of a hindered alkyl, silyl, or aryl group on the C–C triple bond.

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Supplementary Material Available: General experimental procedure for all products (4 pages).

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