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Palladium-Catalyzed Heteroannulation of Internal Alkynes by Vinylic Halides

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Abstract

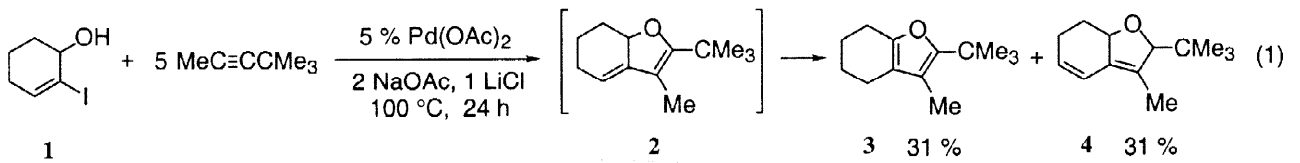
A number of heterocycles have been synthesized regioselectively in good yields by treating appropriate functionally-substituted vinylic halides with internal alkynes in the presence of a palladium catalyst.

Keywords: palladium and compounds; halogens and compounds; annulation.

We have previously reported the synthesis of indoles [1], indenones [2], isocoumarins [3], benzofurans [3], benzopyrans [3] and 1,2-dihydroisoquinolines [3] by the palladium-catalyzed annulation of internal alkynes with 2-iodoanilines, 2-iodobenzaldehydes, methyl 2-iodobenzoates, 2-iodophenols, 2-iodobenzylic alcohols and 2-iodobenzylic amides, respectively. Very recently, we succeeded in synthesizing α-pyrones by employing vinylic halides containing neighboring ester functionality [4]. With this success, we decided to explore the possibility of preparing various oxygen- and nitrogen-containing heterocycles by the palladium-catalyzed annulation of internal alkynes using suitably substituted *vinylic* halides. Here we report the preliminary results of that study (see Table 1).

The starting materials for this study are easily prepared. Iodides **1** and **5** were prepared by the $NaBH_4$ reduction of 2-iodocyclohexenone or 2-iodo-4,4-dimethylcyclohexenone [5] in the presence of $CeCl_3$. Bromide **10** [6] was prepared by the reaction of methyl 2-bromo-1-cyclohexenylcarboxylate with MeMgBr. Tosylamides **13**, **16**, **18** and **20** were prepared by the Mitsunobu reaction of the corresponding alcohols with TsNHBoc, followed by cleavage with trifluoroacetic acid in CH_2Cl_2 [7]. These alcohols were prepared by the $NaBH_4$ reduction of cyclohexylideneiodoacetaldehyde [8] in the presence of $CeCl_3$ and the DIBAL reduction of the corresponding methyl 2-iodo-alkenoates, prepared by organocuprate addition to 3-substituted propynoates and subsequent quenching with I_2 [9].

When iodide **1** was reacted with 5 equiv. of 4,4-dimethyl-2-pentyne in the presence of 5 mol % $Pd(OAc)_2$, 2 equiv. of NaOAc, and 1 equiv. of LiCl at 100 °C in DMF (5 ml/0.25 mmol of vinylic halide) for 24 h, compounds **3** and **4** were obtained in 62% yield as an inseparable 1:1 mixture, presumably via isomerization of intermediate **2** (eq. 1). The



1 2 3 31 % 4 31 %

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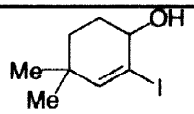
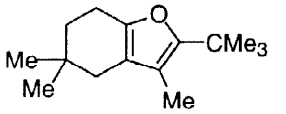
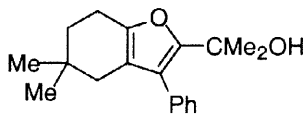
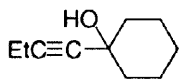
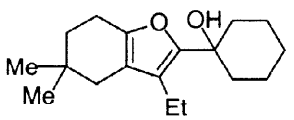
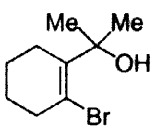
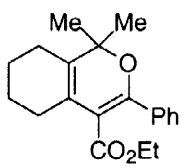
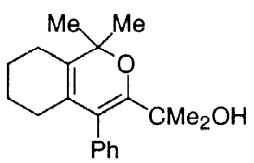
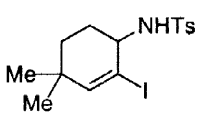
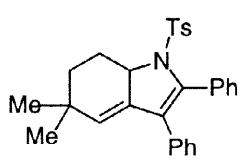
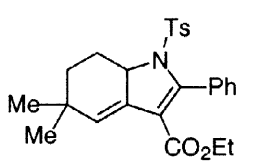
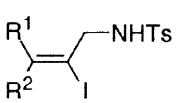
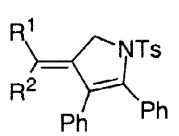
Table 1. Synthesis of Heterocycles via Pd-Catalyzed Annulation of Internal Alkynes by Vinylic Halides [a].

Entry	Halides	Alkyne [b] time (h)	Product	% Yield [c]
1	 **5**	$MeC{\equiv}CCMe_3$ 24	 **6**	69
2	**5**	$PhC{\equiv}CCMe_2OH$ 52	 **7**	72
3	**5**	 24	 **9**	51
4	 **10**	$PhC{\equiv}CCO_2Et$ 84	 **11**	61
5	**10**	$PhC{\equiv}CCMe_2OH$ 168	 **12**	48
6	 **13**	$PhC{\equiv}CPh$ 7	 **14**	78
7	**13**	$PhC{\equiv}CCO_2Et$ 5	 **15**	64
		$PhC{\equiv}CPh$		
8	**16** R^1, R^2 = -$(CH_2)_5$	8	**17**	58
9	**18** $R^1 = R^2$ = Me	10	**19**	77
10	**20** R^1 = Me, R^2 = Ph	10	**21**	61

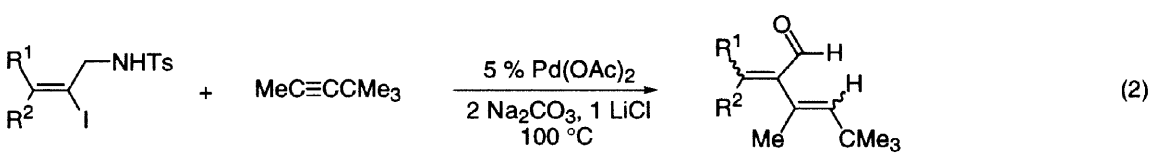
[a]. All reactions were run at 100 °C using 0.25 mmol of halide in the presence of 5 mol % $Pd(OAc)_2$, 1 equiv. of LiCl, and a certain amount of the base in 5 ml of DMF. Entry 1, NaOAc (2 equiv.); entries 2-3, NaOAc (4 equiv.); entries 4-5, Na_2CO_3 (2 equiv.); entries 6-10, Na_2CO_3 (2 equiv.). [b]. 2 Equivalents of alkyne were used, except 4,4-dimethyl-2-pentyne (5 equiv.). [c]. Yields refer to isolated yields. All of the compounds gave satisfactory ^1H NMR, ^{13}C NMR, HRMS and IR spectra.

formation of **4** is apparently due to a 1,5-hydrogen shift in intermediate **2**. Indeed, the reaction of iodide **5**, which lacks the hydrogen necessary for a 1,5-hydrogen shift, with 4,4-dimethyl-2-pentyne under the same reaction conditions afforded furan **6** in 69% yield (Table 1, entry 1). The reaction of iodide **5** with 2-methyl-4-phenyl-3-butyn-2-ol afforded the furan **7** and the initial unisomerized product (**8**) as an inseparable 83:17 mixture in 72% yield. To improve the selectivity of this reaction, the reaction was carried out using different amounts (2-4 equiv) of NaOAc and Na_2CO_3 for various reaction times (10-52 h). Only compound **7** was obtained in 73% yield by employing 4 equiv. of NaOAc for 52 h (entry 2). The reaction using 2 equiv. of Na_2CO_3 for 24 h was intriguing, since the presence of Na_2CO_3 actually inhibited the isomerization process and reversed the product ratio (73% yield, **7**:**8** = 13:87). Applying the optimal isomerization conditions (4 equiv. of NaOAc) to the reaction of iodide **5** and 1-(1-butynyl)cyclohexanol resulted in the formation of furan **9** in 51% yield (entry 3).

Pyrans are also accessible in fair to good yields from the reaction of internal alkynes with 2-(2-bromo-1-cyclohexenyl)-2-propanol (entries 4 and 5) using 1 equiv. of Na_2CO_3. Employing a vinylic bromide significantly decreased the reaction rate and also gave slightly lower yields.

The synthesis of nitrogen heterocycles was next examined. We had envisioned that substrate **13** would react with internal alkynes using NaOAc as the base to form pyrroles in analogy with the furan chemistry. However, reacting iodide **13** with diphenylacetylene under the NaOAc conditions gave a 55 % yield of a complex mixture, consisting mainly of unisomerized product and no pyrrole. Fortunately, since the nitrogen heterocycle was more difficult to isomerize and Na_2CO_3 appeared to inhibit isomerization in our furan chemistry, we were able to cleanly obtain a 78 % yield of the unisomerized product **14** using 2 equiv. of Na_2CO_3 as the base (entry 6). The regioselective reaction of this same sulfonamide with ethyl phenylpropiolate gave similar results (entry 7). Acyclic sulfonamides **16**, **18** and **20** also afforded unisomerized products **17**, **19** and **21** in 58, 77 and 61% yields, respectively, when reacted with diphenylacetylene under similar reaction conditions (entries 8-10).

Interestingly, the reaction of sulfonamides **16**, **18** and **20** with 4,4-dimethyl-2-pentyne afforded unsaturated aldehydes **22-24** in 55, 56 and 73% yields as inseparable 84:16, 89:11 and 57:18:17:8 mixtures of all possible stereoisomers about the two double bonds (eq. 2). No attempt was made to identify each isomer.



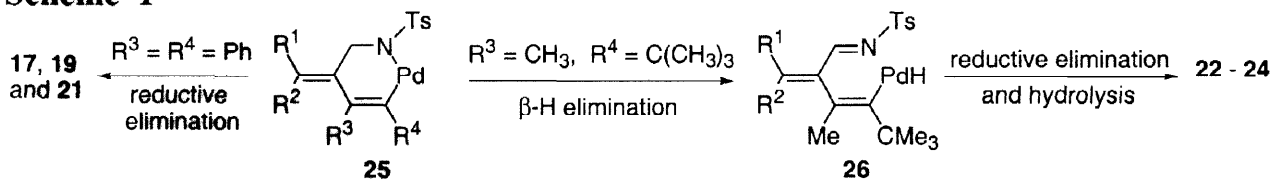
(2)

16 R^1, R^2 = -$(CH_2)_5$-	24 h	**22** 55% (84 : 16)
18 R^1 = R^2 = Me	20 h	**23** 56% (89 : 11)
20 R^1 = Me, R^2 = Ph	18 h	**24** 73% (57 : 18 : 17 : 8)

The mechanism of this latter transformation is rather interesting (Scheme 1). Similar to the formation of other products in this study, the reactions of sulfonamides **16**, **18** and **20** with diphenylacetylene or 4,4-dimethyl-2-pentyne presumably afford intermediate **25** by a sequence involving (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst, (2) oxidative addition of the starting halide to Pd(0), (3) vinylpalladium coordination to the alkyne and subsequent insertion of the alkyne to form a new vinylpalladium intermediate, and (4) attack of the negatively charged nitrogen nucleophile on the vinylpalladium intermediate to form the six-membered palladacycle **25** (Scheme 1). Apparently, when R^3 = R^4 = Ph, intermediate **25** undergoes reductive elimination to afford products **17**, **19** and **21**. However, when R^3 = Me and R^4 = CMe_3, intermediate **25** apparently undergoes β-hydride elimination to afford

intermediate **26**, which upon subsequent reductive elimination affords products **22-24**. The reason for this difference is not clear. However, this is consistent with the fact that our previous yields from the annulation of internal alkynes by functionally-substituted aryl halides are consistently high when diphenylacetylene is employed, presumably due to the easy reductive elimination of intermediates like **25**. Since the addition of organopalladium intermediates to 4,4-dimethyl-2-pentyne is generally highly regioselective [10], the mixtures of isomers **22-24** observed are probably formed by either (1) base-catalyzed isomerization of the α,β-unsaturated aldehydes formed, and/or (2) non-stereospecific reductive elimination of intermediate **26**. We have not attempted to ascertain which path is involved.

Scheme 1



As with our previous chemistry, this annulation process is highly regioselective for alkynes containing hindered alkyl, trialkylsilyl, or other similar groups with a quaternary center. Unfortunately, high-yielding, clean reactions are generally limited to these types of alkynes. An exception to this generality is the regioselective annulation of various substrates onto ethyl phenylpropiolate (entries 4 and 7). The products are assumed to have the more sterically-demanding group in the 2-position of these ring systems in accordance with the pattern established in our previous alkyne addition reactions.

The foregoing study demonstrates that a useful synthesis of unsaturated heterocycles has been developed using the palladium-catalyzed annulation of sterically-hindered internal alkynes. The procedure utilizes easily synthesized starting materials. The reaction proceeds regioselectively under relatively mild conditions and gives good yields. The reaction of tosylamides **16**, **18** and **20** with 4,4-dimethyl-2-pentyne affords unexpected α,β-unsaturated aldehydes **22-24**. Under appropriate reaction conditions, some products can be easily isomerized to produce highly substituted furans. Unfortunately, we are unable to obtain pyrroles in an analogous fashion and similar reactions with comparable acyclic vinylic halides have often produced either complex mixtures or no identifiable products at all.

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References

[1] Larock RC, Yum EK J. Am. Chem. Soc. 1991;113:6689.
[2] Larock RC, Doty MJ, Cacchi S J. Org. Chem. 1993;58:4579.
[3] Larock RC, Yum EK, Doty MJ J. Org. Chem. 1995;60:3270.
[4] Larock RC, Han X, Doty MJ Tetrahedron Lett., submitted.
[5] Johnson CR, Adams JP, Braun MP, Senanayake CBW, Wovkulich PM, Uskokovic MR Tetrahedron Lett. 1992;33:917.
[6] Abad A, Arno M, Pedro JR, Seoane E J. Chem. Soc., Perkin Trans. 1 1983;2471.
[7] Henry JR, Marcin LR, McIntosh MC, Scola PM, Harris DG, Weinreb SM Tetrahedron Lett. 1989;30:5709.
[8] Antonioletti R, D'Auria M, Piancatelli G, Scettri A Tetrahedron Lett. 1981;22:1041.
[9] Klein J, Levene R J. Chem. Soc., Perkin Trans. II, 1973;1971.
[10] Larock RC, Doty MJ, Tian Q, Zenner JM J. Org. Chem. 1997;62:7536.