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Palladium-catalyzed ring expansion reaction of 1-alkynylcyclobutanols with aryl iodides: an efficient route to 2-disubstituted methylenecyclopentanones

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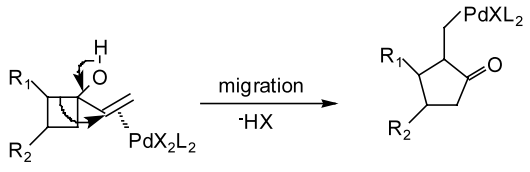
Abstract—The reaction of 1-alkynylcyclobutanols with aryl iodides in the presence of $Pd(OAc)_2$ and Et_3N in acetonitrile at 80°C for 24 h gives 2-disubstituted methylenecyclopentan-1-ones in modest to good yields. The tandem insertion-ring expansion process proceeds via the formation of an alkynyl π-complex, followed by migration of a carbon–carbon bond of the *tert*-alkanol to form the cyclopentanones stereoselectively.

Palladium-promoted ring expansion reactions of 1-alkenyl or 1-alkynyl cyclobutanols to the construction of five-membered ring systems have been successfully applied to the synthesis of biologically active natural products.[1,2] (Scheme 1) Ihara and Fukumoto et al. have developed a cascade insertion-ring expansion reaction of allenylcyclobutanols with aryl iodides.[3] The reaction generates a new carbon-carbon bond along with rearrangement of the four-membered ring system in a one-pot process, and constitutes a potentially useful synthetic method for the efficient synthesis of natural products. Recently, we reported a powerful palladium-catalyzed hydroarylation of aryl iodides with trimethylsilylacetylenes and disubstituted alkynes to give the diarylacetylenes and triarylethylenes.[4] Our approach to a tandem addition-ring expansion reaction involves the application of the recently discovered hydroarylation conditions employing Pd(0) or Pd(II) to 1-alkynylcyclobutanols and aryl iodides. Now, we disclose a new strategy for the synthesis of 2-arylidenecyclopentanones in a one-step process.



Scheme 1.

Tandem reactions were first studied using 1-[2-(4-tolyl)ethynyl]cyclobutanol (**1a**)[5] and iodobenzene (**2a**).Treatment of **1a** (0.3 mmol) and **2a** (0.6 mmol) with 5 mol% $Pd(dba)_2$ and triethylamine (1.5 mmol) in acetonitrile at 80°C for 24 h under nitrogen provided the α-arylidenecyclopentanone **3aa** in 50% yield (Table 1, entry 1).[6]

When the catalyst was replaced by other palladium catalysts, such as $Pd(OAc)_2$, $Pd(OCOCF_3)_2$, $Pd(CH_3CN)_2Cl_2$, under the same reaction conditions, the same product was isolated in 68, 40 and 48% yields, respectively (entries 2–4). The results show that $Pd(OAc)_2$ is the most efficient catalyst for the successive addition–rearrangement of 1-alkynylcyclobutanols. As a solvent for this reaction, acetonitrile was found to be more efficient than MeOH, THF, DMF and 1,4-dioxane. Triethylamine was the base of choice, and other bases, such as K_2CO_3, NaOAc, Ag_2CO_3 and pyridine, were found to be less efficient. Thus, various aryl iodides were reacted with 1-[2-(4-tolyl)ethynyl]-cyclobutanol **1a** using $Pd(OAc)_2$ as the catalyst and triethylamine as the base to give the 2-arylidenecyclopentanones **3** in 50–75% yields. The results are summarized in Table 1. 4-Tolyl iodide **2b** and 4-methoxyphenyl iodide **2c** afforded the corresponding cyclopentanones **3ab** and **3ac** in 70 and 50% yields, respectively (entries 5, 6). The reactions of 2-

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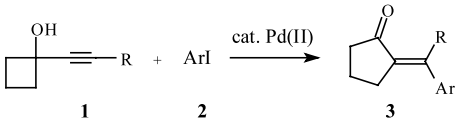
Table 1. Palladium-catalyzed sequential addition-rearrangement of 1-(2-substituted ethynyl)cyclobutanols with aryl iodides

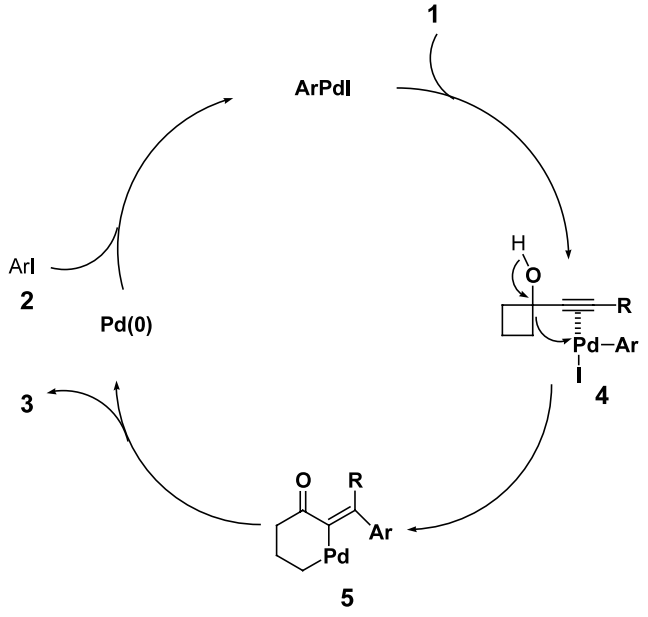


1 2 3

Entry	1-Ethynylcyclobutanols	Aryl iodides	Pd catalyst	Products[a] (yield, %)
1	**1a** (R = 4-tolyl)	**2a** (Ar = phenyl)	$Pd(dba)_2$	**3aa** (50%)
2	**1a**	**2a**	$Pd(OAc)_2$	**3aa** (68%)
3	**1a**	**2a**	$Pd(OCOCF_3)_2$	**3aa** (40%)
4	**1a**	**2a**	$Pd(CH_3CN)_2Cl_2$	**3aa** (48%)
5	**1a**	**2b** (Ar = 4-tolyl)	$Pd(OAc)_2$	**3ab** (70%)
6	**1a**	**2c** (Ar = 4-methoxyphenyl)	$Pd(OAc)_2$	**3ac** (50%)
7	**1a**	**2d** (Ar = 2-tolyl)	$Pd(OAc)_2$	**3ad** (74%)
8	**1a**	**2e** (Ar = 2,3-dimethylphenyl)	$Pd(OAc)_2$	**3ae** (70%)
9	**1b** (R = phenyl)	**2a**	$Pd(OAc)_2$	**3ba** (73%)
10	**1b**	**2b**	$Pd(OAc)_2$	**3bb** (65%)
11	**1b**	**2c**	$Pd(OAc)_2$	**3bc** (49%)
12	**1b**	**2d**	$Pd(OAc)_2$	**3bd** (74%)
13	**1b**	**2e**	$Pd(OAc)_2$	**3be** (75%)
14	**1c** (R = *n*-butyl)	**2b**	$Pd(OAc)_2$	**3cb** (30%[b])

[a] Yields refer to isolated yields. All of the compounds gave satisfactory ^1H, ^{13}C NMR and MS spectra data.
[b] Reacted for 48 h.

tolyl iodide **2d** and 2,3-dimethylphenyl iodide **2e** produced **3ad** and **3ae** in 74 and 70% yields, respectively (entries 7, 8), which indicated that steric hindrance has little effect on this addition reaction. However, when 2-iodopyridine was used in this reaction, no reaction took place and most of the starting materials were recovered. 1-[2-(Phenyl)ethynyl]cyclobutanol (**1b**) was prepared. The reaction of **1b** with various aryl iodides under the optimal reaction conditions gave the products in 49–75% yields. Iodobenzene gave the 2-disubstituted methylenecyclopentan-1-one **3ba** in 73% yield (entry 9). 4-Tolyl iodide and 4-methoxyphenyl iodide afforded the corresponding cyclopentanones **3bb** and **3bc** in 65 and 49% yields, respectively (entries 10, 11). 2-Tolyl iodide and 2,3-dimethylphenyl iodide gave the cyclopentanones **3bd** and **3be** in 74 and 75% yields, respectively (entries 12, 13). The structure of **3bd** was unambiguously determined by X-ray crystallographic analysis.[7] It should be noted that the ring expansion process proceeds in a stereoselective manner. 1-(1-Hexynyl)cyclobutanol (**1c**) was also examined. The reaction took place much slower and required 48 h to give the product **3cb** in only 30% yield (entry 14).



Scheme 2.

A mechanism for this cascade insertion-rearrangement reaction is proposed in Scheme 2. The formation of the product can be explained as follows; first, the oxidative addition of the aryl iodide to a palladium complex gives an arylpalladium intermediate, which coordinates to the carbon–carbon triple bond of **1** to form a σ-arylpalladium complex and produce the η^2-palladium complex. Next, the ring transformation of **4** gives the σ-alkylpalladium complex **5** in a stereoselective fashion.[3] Finally, reductive elimination of Pd(0) from the resultant σ-alkylpalladium complex **5** provides the product **3**.

In conclusion, the tandem insertion-ring expansion of 1-alkynylcyclobutanols provides a one-step synthesis of α-disubstituted methylenecyclopentanones. This ring expansion reaction proceeds in a stereoselective manner.

Acknowledgements

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References

1. For some recent works on palladium-catalyzed ring expansion of cyclobutanols: see (a) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett*. **1985**, *26*, 2503–2506; (b) Greene, A. E.; Luche, M.-J.; Serra, A. A. *J. Org. Chem*. **1985**, *50*, 3957–3962; (c) Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc*. **1987**, *109*, 7908–7910; (d) Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1990**, *112*, 291–296; (e) Nemoto, H.; Miyata, J. M.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363–10374; (f) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem*. **1997**, *62*, 7850–7857.
2. Recently, Uemura et al. reported a palladium-catalyzed oxidative ring cleavage reaction of cyclobutanols: (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 2645–2646; (b) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **1999**, *121*, 11010–11011; (c) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc*. **2000**, *122*, 12049–12050.
3. (a) Nemoto, H.; Miyata, J.; Yoshida, M.; Raku, N.; Fukumoto, K. *J. Org. Chem*. **1997**, *62*, 6450–6451; (b) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett*. **1999**, *40*, 8583–8586; (c) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett*. **2000**, *41*, 5089–5092.
4. Wu, M.-J.; Wei, L.-M.; Lin, C.-F.; Leou, S.-P.; Wei, L.-L. *Tetrahedron* **2000**, *57*, 7839–7844.
5. Compounds **1a–c** were prepared from the cyclobutanone as follows: to a dry 150-mL round-bottomed under nitrogen atmosphere was added the corresponding terminal alkyne (15 mmol) and tetrahydrofuran (15 mL). The solution was cooled to −78°C and *n*-butyllithium (1.6 M in hexane, 7.5 mL) was added dropwise by syringe. After stirring for 30 min, a solution of cyclobutanone (10 mmol) in THF (5 mL) was added dropwise and the mixture stirred at the same temperature for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine. The residue upon workup was chromatographed on silica gel, using *n*-hexane–EtOAc (10:1 v/v) as eluent to give the cyclobutanols **1a–c** as colorless oils. Selected spectral data for 1-[2-(4-tolyl)ethynyl]cyclobutanol: **1a**, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (dd, 2H, $J=8.0$, 1.7 Hz), 7.10 (d, 2H, $J=8.4$ Hz), 2.84 (b, 1H,), 2.37–2.53 (m, 4H), 2.34 (s, 3H), 1.82–1.91 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 131.5, 128.9, 119.6, 91.9, 83.4, 68.2, 38.6, 21.3, 12.9; EI(MS) m/z (rel. intensity) 186 (M^+, 2), 158(89), 143(41), 115(100).
6. *Typical experimental procedure for the addition-ring expansion reaction*. A slurry of the 1-alkynylcyclobutanol **1a** (0.3 mmol), *p*-iodotoluene **2b** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), Et_3N (1.5 mmol) in CH_3CN (8 mL) was stirred for 24 h at 80°C. The reaction mixture was filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed three times with a small amount of EtOAc and the combined solution was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel using *n*-hexane–EtOAc (20:1 v/v) as eluent to give the cyclopentanone **3ab** (70%) as a light yellow solid. Mp: 149–150°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10–7.14 (m, 4H), 7.07 (dd, 2H, $J=6.4$, 1.8 Hz), 7.00 (dd, 2H, $J=6.4$, 1.8 Hz), 2.80 (t, 2H, $J=7.0$ Hz), 2.36 (s, 3H), 2.36 (t, 2H, $J=8.0$ Hz), 2.35 (s, 3H), 1.91 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.6, 148.6, 139.2, 138.4, 137.6, 137.3, 133.6, 129.7, 129.5, 128.6, 128.5, 39.9, 33.2, 21.4, 21.3, 20.5; Anal. calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.75; H, 7.36.
7. Crystal data for **3bd**: $C_{19}H_{18}O$; $M=262.33$ g/mol, crystal size: 0.40×0.30×0.25 mm, triclinic, space group P-1, $\lambda=0.71073$ Å, $a=9.3796(9)$ Å, $b=9.4887(9)$ Å, $c=9.5587(9)$ Å, $\alpha=87.687(2)°$, $\beta=85.472(2)°$, $\gamma=60.466(2)°$, $V=737.87(12)$ Å^3, $Z=2$, $D=1.181$ Mg/m^3. $\mu=0.071$ mm^{-1}, $T=295(2)$ K, θ range: 2.14–27.5°, reflections collected: 7461, independent reflections: 3389 ($R_{int}=0.0208$), refinement method: full-matrix least-square on F^2, final R values[I>2σ(I)]: $R_1=0.0746$, w$R_2=0.2185$. Diffractometer: Bruker SMART APEX. Crystallographic data (excluding structure factors) for this structure have been deposited at the Cambridge Crystallographic Data centre as supplementary publication no. CCDC-190286, and may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).