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Palladium-catalyzed cascade reactions of benzyl halides with *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide

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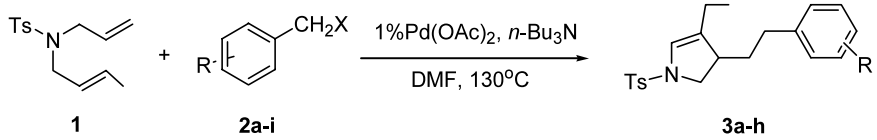
Abstract—Reaction of benzyl halides with *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide **1** in the presence of a palladium catalyst afforded dihydropyrroles **3** in moderate to excellent yields. It is proposed that the cyclic products were formed via a palladium-catalyzed cascade cyclization-coupling process.

Heterocyclic nuclei are present in many pharmacologically active compounds.[1] Many synthetic methods for the construction of cyclic compounds have been developed, including ring-closing metathesis,[2] cyclic cascade reactions,[3] and Mizoroki–Heck reactions. [4] Palladium-catalyzed annulation technology has become one of the most powerful tools in the construction of heterocyclic compounds. Aryl or olefinic halides have been used as starting materials in various cases, but few examples of palladium-catalyzed annulation reactions of alkyl halides are known. In our continuing research on palladium-catalyzed Heck reactions of benzyl halides with olefins,[5] we report here a novel palladium-catalyzed reaction of benzyl halides with a diene. Thus, benzyl chloride **2a** reacted with *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide **1**, prepared according to the literature,[6] in the presence of palladium acetate in DMF at 120–130°C for 15–16 h, to give an unexpected cyclic product having a dihydropyrrole ring, as the only identifiable product. Further studies, using various substituted benzylic halides, confirmed that the reaction between *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide with benzylic halides is a novel and general palladium-catalyzed process (Scheme 1).

The products were isolated by flash column chromatography on silica gel. As indicated in Table 1, yields were dependent on the substituents on the phenyl ring. Benzylic chlorides with electron-donating substituents, such as a methyl group (entries 2–4), led to smooth reactions and afforded higher yields. Electron-withdrawing groups such as carboxylate (entry 8) and bromine (entry 7) suppressed the reaction. It is believed that the cyclic products were formed via a cascade cyclization-coupling process.

The reaction must involve at least two additions of organopalladium intermediates to the double bonds (Scheme 2). Once the benzylic palladium species is formed, it reacts with one of the double bonds of the diene substrate to form a new palladium intermediate, which reacts with the other double bond intramolecularly accomplishing the formation of a ring in a cascade. Although Negishi et al.[7] reported some interesting examples of intramolecular Heck reactions of benzyl halides, the reaction we report here is the first example of a cascade reaction of benzylic halides with olefins via intermediates in which β-hydrogens are available. Palladium-catalyzed rearrangement of the double bond affords the products.



1 **2a-i** **3a-h**

Scheme 1.

Keywords: palladium; Heck reaction; benzyl halides; cyclization; cascade reaction.
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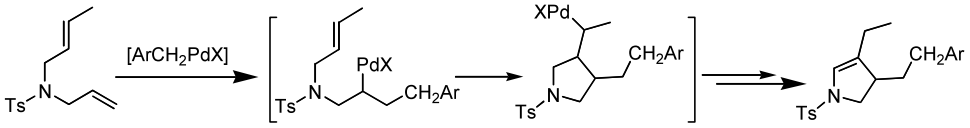
Table 1. Reactions of *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide **1** with benzylic halides **2a–i**

Entry	X	R	Temp. (°C)	Time (h)	Product	Yield (%)[a]
1	Cl	H	120	15	**3a**	76
2	Cl	*p*-CH_3	120	15	**3b**	71
3	Cl	*o*-CH_3	120	15	**3c**	66
4	Cl	*m*-CH_3	120	15	**3d**	68
5	Cl	*o*-Cl	120	15	**3e**	59
6	Cl	*p*-Cl	120	15	**3f**	62
7	Cl	*p*-Br	130	16	**3g**	51
8	Cl	*m*-$COOCH_3$	130	16	**3h**	47
9	Br	H	120	15	**3a**	72

[a] Isolated yield of analytically pure product.



Scheme 2.

Typical procedure for the preparation of 3a. A dried Schlenk flask was evacuated and filled with nitrogen, then charged with *N*-allyl-*N*-(2-butenyl)-*p*-toluenesulfonamide (1.01 g, 5 mmol), benzyl chloride (0.95 g, 7.5 mmol), tributylamine (1.8 mL), $Pd(OAc)_2$ (12 mg, 0.05 mmol, 1 mol%), and the appropriate amount of DMF to give a yellow solution. The reaction mixture was heated at 120–130°C with stirring. The reaction mixture was cooled to rt after 15–16 h and the resultant yellow–orange mixture was diluted with Et_2O (10 mL). The mixture was washed with H_2O (15 mL) and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 6:1) to give **3a** as a white solid. Yield: 1.35g, 76%. Anal. calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.77; H, 6.92; N, 3.94%. IR (KBr): 3026 (m), 2959 (w), 2929 (s), 2875 (w), 1712 (v), 1598 (m), 1494 (m), 1452 (m), 1344 (s), 1163 (m), 816 (m), 749 (m), 697 (m), 664 (s), 589 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 355 (M^+, 6), 249 (53), 155 (40), 110 (41), 91 (100). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.64$ (d, 2H, $J = 8.0$ Hz, ArH), 7.24 (d, 2H, $J = 8.0$ Hz, ArH), 6.95–7.21 (m, 5H, ArH), 6.01 (s, 1H, N-CH=C), 3.60 (t, 1H, N-CH_2), 3.18 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 6.0$ Hz, N-CH_2), 2.58–2.60 (m, 1H), 2.34–2.36 (m, 1H), 2.33 (s, 3H, CH_3), 2.19–2.25 (m, 1H), 1.93–1.98 (m, 1H), 1.78–1.84 (m, 1H), 1.60–1.63 (m, 1H), 1.04–1.09 (m, 1H), 0.95 (t, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 144.04$, 141.81, 133.19, 132.29, 129.95, 128.77, 128.56, 128.15, 126.34, 123.95, 53.02, 44.46, 34.49, 33.07, 21.88, 20.07, 12.46.

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