Pd-mediated synthesis of substituted benzenes fused with carbocycle/heterocycle†‡

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A new Pd-catalyzed one-pot multicomponent coupling reaction for the construction of benzene ring fused with carbocycle or heterocycle under a Cu-free condition is described.

Polyfunctionalized benzenes fused with a carbocycle or heterocycle play an important role in organic chemistry, not only as key synthons in many bioactive compounds and drugs,[1] but also as useful intermediates widely used in industry as well as the laboratory. For this reason, there is a continued interest in the development of new multicomponent coupling reactions that allow assembly of multiply substituted benzene in a highly regioselective manner. Among the many different approaches to polysubstituted benzenes, the transition-metal mediated multicomponent coupling *e.g.* [2 + 2 + 2]-cyclotrimerization of alkynes[2] or [4 + 2]-cyclodimerization of conjugated enynes[3] is particularly attractive. Recently, regioselective construction of benzene ring using a Sonogashira coupling–[4 + 2]-benzannulation strategy has been reported.[4] We envisioned that compounds containing the 2-alkynyl enone moiety (**A**, Fig. 1) in the presence of a terminal alkyne might also undergo a transition metal-mediated [4 + 2]-benzannulation, affording a general method for the regioselective synthesis of benzene fused with carbocyclic/heterocyclic structure, that has rarely been reported.[4a]

This unique intermolecular benzannulation process is particularly attractive, because by choosing an appropriate enynone partner a carbocycle or heterocycle of specific interest can be fused with the benzene ring, which allows for considerable versatility, since a variety of enynone derivatives can be generated from the corresponding α-haloketones (Fig. 2).

Recently, we have reported that the palladium [$(PPh_3)_2PdCl_2$] catalyzed reaction of 3-halo (thio)flavones with terminal alkynes affords the corresponding 3-enynyl (thio)flavones[5a,b] particularly under a Cu-free condition.[5c] More recently, we examined the reaction between 2-iodo-2-cyclohexenone (**1a**) with 2-methyl-3-butyn-2-ol (**2a**) under a similar Cu-free condition (Scheme 1).

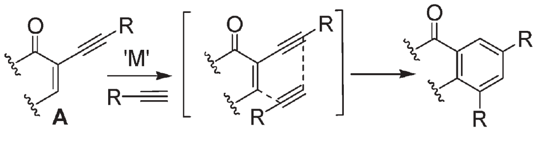


Fig. 1 Synthesis of polysubstituted benzenes.

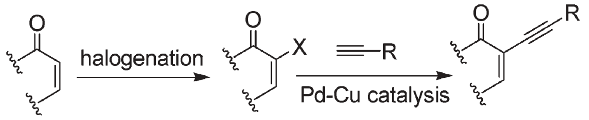
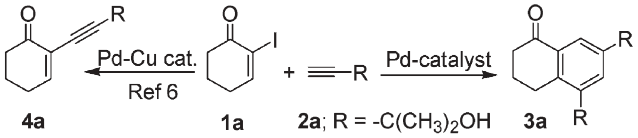


Fig. 2 Synthesis of enynone derivatives.



Scheme 1 Pd-catalyzed reactions of 2-iodo-2-cyclohexenone (**1a**) with terminal alkynes.

Very interestingly, the reaction gave an aromatic compound **3a** but not the Sonogashira product[6] **4a**. Compound **3a** showed an intense molecular ion peak at *m*/*z* 263.0 (M^+, 100%) in the mass spectra and gave signals at δ 8.09 and 7.91 in the ^1H NMR spectra due to the aromatic protons. Additionally, the signal at δ 198.4 in the ^{13}C NMR (1662 cm^{-1} in IR) spectra identified **3a** as a 1-tetralone derivative. This was supported by the molecular structure of **3b** (R = 1-hydroxy cyclohexyl) confirmed by X-ray analysis (Fig. 3).[7]

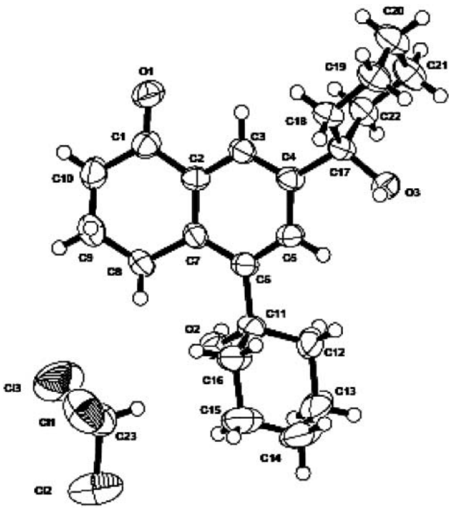


Fig. 3 X-Ray crystal structure of **3b** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.

Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad, 500049, India. E-mail: manojitpal@drreddys.com; Fax: 91 40 2304 5438; Tel: 91 40 2304 5439

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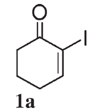
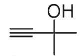
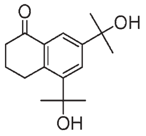
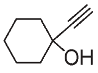
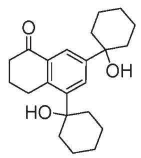
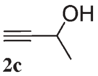
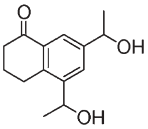
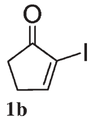
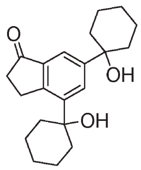
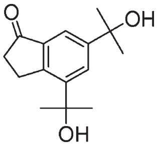
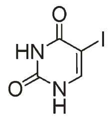
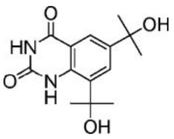
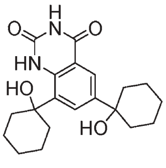
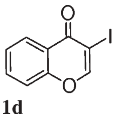
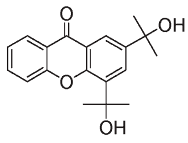
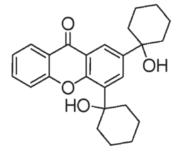
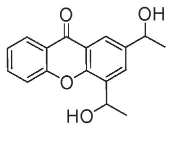
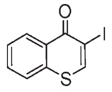
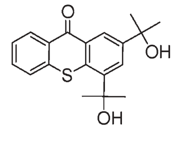
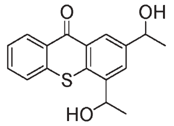
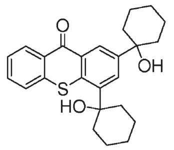
‡ Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, crystallography and *in vitro* testing. See DOI: 10.1039/b612770c

Table 1 Pd-mediated synthesis of substituted benzenes[a]

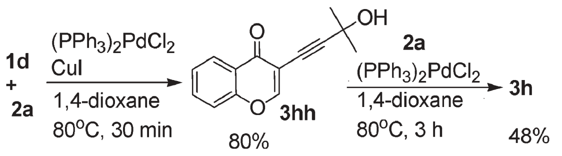
Entry	Haloenone	Alkyne	Product		Yield (%)
1	 **1a**	 **2a**		**3a**	75
2	**1a**	 **2b**		**3b**	80
3	**1a**	 **2c**		**3c**	62
4	 **1b**	**2b**		**3d**	50
5	**1b**	**2a**		**3e**	52
6	 **1c**	**2a**		**3f**	65
7	**1c**	**2b**		**3g**	58
8	 **1d**	**2a**		**3h**	77
9	**1d**	**2b**		**3i**	67
10	**1d**	**2c**		**3j**	62
11	 **1e**	**2a**		**3k**	52
12	**1e**	**2c**		**3l**	62
13	**1e**	**2b**		**3m**	78

[a] All reactions were carried out by using **I** (0.9 mmol), **2** (0.27 mmol), $PdCl_2(PPh_3)_2$ (0.036 mmol), Et_3N (7.2 mmol) in DMF (for entries 1, 6, 8 and 11) or 1,4-dioxane at 80 °C for 3–5 h under nitrogen.

We then investigated the reaction between **1a** and **2a** under various conditions to find the optimum condition for obtaining this unprecedented reaction product in higher yields. Among the catalysts we examined, $(PPh_3)_2PdCl_2$ or $PdCl_2$ in DMF gave best results while the use of 10% Pd/C–PPh_3 or $Pd(OAc)_2$ or $(PPh_3)_4Pd$ also afforded **3a** albeit in low yields. When the reaction was performed in the absence of $(PPh_3)_2PdCl_2$ no product was formed indicating that the Pd-catalyst is needed for the reaction to proceed. The best solvent for the reaction was DMF or 1,4-dioxane and Et_3N was the base of our choice. The preparation of **3a** is representative: A mixture of **1a** (0.9 mmol), $(PPh_3)_2PdCl_2$ (0.036 mmol) and Et_3N (7.2 mmol) in DMF (6 mL) was stirred at 25 °C for 5 min under N_2 and **2a** (0.27 mmol) was added slowly. The mixture was stirred at 80 °C for 3 h, and after usual work up the product was isolated by column chromatography (petroleum ether–EtOAc) to afford **3a** in 75% yield (Table 1, entry 1). We then tested the optimized conditions with other terminal alkynes (Table 1, entries 2 and 3). The reaction proceeded well to give 5,7-disubstituted 1-tetralones **3b** and **3c**. Isomeric products such as 6,7-disubstituted 1-tetralones or dimeric product,[4b] which may be formed during the benzannulation process, were not detected. However, the use of 2-iodocyclopent-2-one afforded 1-indanones **3d** and **3c** (Table 1, entries 4 and 5) along with unidentified side products. The use of other appropriate halides afforded quinazoline-2,4-dione, xanthen-9-one and thioxanthen-9-one derivatives, respectively (Table 1, entries 6–13). Notably, the reaction of 1-ethynyl-4-methylbenzene with **1a** provided the corresponding Sonogashira product *i.e.* 2-*p*-tolylethynylcyclohex-2-enone in 30% yield along with other side products.[8]

Mechanistically, the reaction seems to proceed *via* generating 2-alkynyl enones (**A**) *in situ* according to a Cu-free Sonogashira pathway[5a,c] followed by regioselective [4 + 2]-benzannulation,[3c,9] perhaps aided by the electron-withdrawing effect of the carbonyl group, involving a second molecule of terminal alkyne (Fig. 1). To prove the intermediacy of **A**, the reaction of **1d** with **2a** was carried out for 1.5 h, which afforded a 1 : 1 mixture of **3h** and 3-alkynylflavone (**3hh**). However, **3hh** was consumed after another 1.5 h producing **3h** as the sole product. Additionally, **3hh** (prepared *via* Sonogashira coupling of **1d** with **2a**) afforded **3h** when reacted separately with **2a** under the same condition (Scheme 2).

In summery, a new catalytic approach to benzo derivatives of carbo- and heterocycles has been developed through the sequential



Scheme 2 Pd-catalyzed reactions of **1d** with terminal alkyne **2a**.

coupling–benzannulation of α-haloenone with terminal alkynes. This one-pot Cu-free process was found to be general when alkyl substituted alkynes were used affording an array of compounds of potential biological significance,[10] the preparation of which may be tedious *via* other methods.

We thank Dr R. Rajagopalan, Prof. J. Iqbal, for their encouragement and analytical group for spectral data.

Notes and references

1 See, for example: (*a*) S. Gobbi, A. Rampa, A. Bisi, F. Belluti, P. Valenti, A. Caputo, A. Zampiron and M. Carrara, *J. Med. Chem.*, 2002, **45**, 4931; (*b*) I. K. Kostakis, P. Magiatis, N. Pouli, P. Marakos, A.-L. Skaltsounis, H. Pratsinis, S. Leonce and A. Pierre, *J. Med. Chem.*, 2002, **45**, 2599; (*c*) Q. Chao, L. Deng, H. Shih, L. M. Leoni, D. Genini, D. A. Carson and H. B. Cottam, *J. Med. Chem.*, 1999, **42**, 3860; (*d*) X. Wang, K. F. Bastow, C.-M. Sun, Y.-L. Lin, H.-J. Yu, M.-J. Don, T.-S. Wu, S. Nakamura and K.-H. Lee, *J. Med. Chem.*, 2004, **47**, 5816.

2 For selected references, see: (*a*) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; (*b*) M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; (*c*) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901; (*d*) Y. Yamamoto, J.-I. Ishii, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2004, **126**, 3712.

3 (*a*) S. Saito, Y. Chounan, T. Nogami, T. Fukushi, N. Tsuboya, Y. Yamada, H. Kitahara and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 5350; (*b*) V. Gevorgyan, N. Tsuboya and Y. Yamamoto, *J. Org. Chem.*, 2001, **66**, 2743; (*c*) S. Saito, M. M. Salter, V. Gevorgyan, N. Tsuboya, K. Tando and Y. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 3970, and references therein; (*d*) V. Gevorgyan, A. Takeda, M. Homma, N. Sadayori, U. Radhakrishnan and Y. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 6391.

4 For a sequential one-pot procedure involving Sonogashira coupling and homo-benzannulation for the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones, see: (*a*) T. Kawasaki and Y. Yamamoto, *J. Org. Chem.*, 2002, **67**, 5138; (*b*) C. Xi, C. Chen, J. Lin and X. Hong, *Org. Lett.*, 2005, **7**, 347.

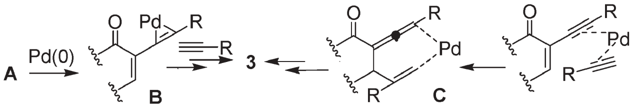
5 (*a*) M. Pal, R. Dakarapu, K. Parasuraman, V. Subramanian and K. R. Yeleswarapu, *J. Org. Chem.*, 2005, **70**, 7179; (*b*) M. Pal, K. Parasuraman, V. Subramanian, R. Dakarapu and K. R. Yeleswarapu, *Tetrahedron Lett.*, 2004, **45**, 2305; (*c*) For our studies on Cu-free Sonogashira coupling, see: M. Pal, K. Parasuraman, S. Gupta and K. R. Yeleswarapu, *Synlett*, 2002, 1976.

6 For Sonogashira coupling of 2-halo-2-cyclohexenone with terminal alkynes in the presence of Cu-salt, see: (*a*) T. Yao, X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 11164. See also:(*b*) M. W. Miller and C. R. Johnson, *J. Org. Chem.*, 1997, **62**, 1582, and references cited therein.

7 *Crystallographic data* for **3b**: single crystal from chloroform, $C_{23}H_{30}O_3\cdot CHCl_3$, M = 461.86, monoclinic, space group $P2_1/c$, a = 12.653(6), b = 16.148(7), c = 11.478(5) Å, β = 93.125(6)°, V = 2341(1) Å^3, Z = 4, D_c = 1.310 Mg m^{-3}, T = 298 K, μ = 4.119 cm^{-1}, 26740 processed reflections, 5278 unique reflections, 2930 observed reflections, R_{int} = 3.87%, and R = 0.090 for the 2930 'observed' reflections and $wR2$ = 0.167 for all 5278 unique reflections. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612770c.

8 One of the side products isolated was identified as 2-(2,4-di-*p*-tolylbut-1-en-3-ynyl)cyclohex-2-enone (see ESI‡).

9 The benzannulation may proceed *via* the interaction of **A** with the Pd(0) species producing a π-complex intermediate **B**, which might act as a nucleophilic diene and undergo (formal) Diels–Alder reaction. Alternatively, this reaction may involve a metallacycle such as **C** as an intermediate.



10 Compounds **3i** and **3m** showed anticancer activity with an average GI_{50} of 14.6 and 7.1 μM, respectively, on a tested panel of cancer cell lines [*e.g.* HT29 (colon), H460 (lung), LoVo (colon)] (see ESI‡).