Tandem C–C coupling – intramolecular acetylenic Schmidt reaction under Pd/C–Cu catalysis†‡

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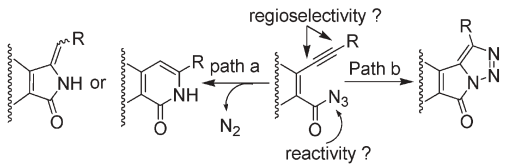
A new one-pot reaction for the regioselective construction of a six-membered fused *N*-heterocyclic ring leading to isoquinolones under Pd/C–Cu catalysis is described.

Transition metal mediated synthesis of nitrogen containing heterocycles *via* addition of an N–H bond across the C–C triple bond has been one of the frontier areas in organic chemistry.[1] This is exemplified by the synthesis of a large variety of structurally diverse *N*-heterocycles and palladium is by far the most utilized metal in these catalytic processes. While the Pd-mediated synthesis of a number of *N*-heterocycles, especially indoles,[2] has been studied extensively, only a few have been reported for the synthesis of 1(2*H*)-isoquinolones.[3] Nevertheless, this heterocycle is one of the basic units found in a wide variety of plant alkaloids, bioactive compounds and drugs.[4] For example, 6-amino-7-chloro-2-(5-methyl-3*H*-imidazol-4-ylmethyl)-2*H*-isoquinolone has been identified as a novel orally active 5-HT_3 antagonist[4a] and 2-{4-[(1-oxo-1,2-dihydroisoquinolin-7-ylmethyl)-prop-2-ynylamino]-benzoylamino}succinic acid showed promising thymidylate synthase (TS) inhibitory activity.[4b] Since TS inhibitors could play a role as potential anticancer agents, we decided to explore the synthesis and anticancer activities of a library of small molecules based on an isoquinolone scaffold.

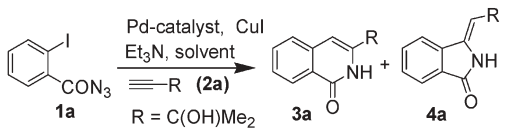
Recently, the union of terminal alkynes and organic azides[5] in the presence of transition metal catalysts to give 1,4-disubstituted 1,2,3-triazoles has shown remarkable applications in organic synthesis.[6] An intramolecular version of this [3 + 2] cycloaddition afforded isoindoline fused with triazoles successfully under appropriate reaction conditions.[6d] On the other hand the reactivity of alkyl azides as nucleophiles toward gold(I)-activated alkynes in an intramolecular cyclization process (acetylenic Schmidt reaction) leading to pyrroles has been studied recently.[7a] The present communication addresses several challenging issues related to the use of acyl azides[7b] (Scheme 1) *e.g.* (i) their reactivity towards transition metal-activated alkynes, (ii) regioselectivity and (iii) the optimal catalyst system. We envisaged that the acyl group of acyl azide might influence the reactivity pattern of azide favouring expulsion of dinitrogen as the reaction proceeds (path a, Scheme 1).



Scheme 1

To this end, we have observed that treatment of 2-iodobenzoyl azide (**1a**) with 2-methylbut-3-yn-2-ol (**2a**) in the presence of a palladium catalyst, CuI and E_3N produced the corresponding 3-substituted-1(2*H*)-isoquinolone (**3a**) as a major product (entries 1–4, Table 1). Among the catalysts we examined, 10% Pd/C–PPh_3 in EtOH gave better results (entry 3, Table 1) although the use of $(PPh_3)_2PdCl_2$ or $(PPh_3)_4Pd$ afforded **3a**, albeit in low yields. When the reaction was performed in the absence of CuI no product was formed, indicating that the Cu-catalyst is needed for the reaction to proceed. On the other hand the reaction gave mainly five-membered ring product (**4a**) in the absence of Pd-catalyst (entry 6, Table 1). Compound **4a** was also isolated as the only product when other solvents were used (entries 7–11, Table 1). Isoquinolone **3a** was distinguished from the isoindolinone **4a** on the basis of their IR spectra. The carbonyl absorption band

Table 1 Pd-mediated coupling of **1a** with terminal alkyne (**2a**)[a]

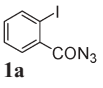
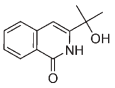
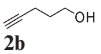
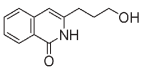
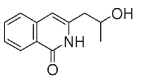
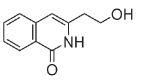
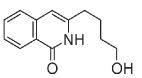
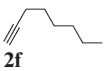
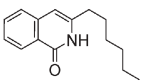
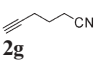
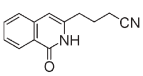
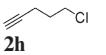
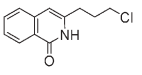
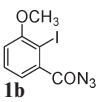
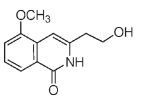
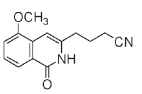
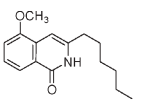
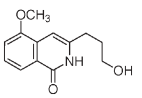
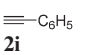
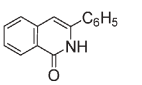
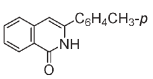


Entry	Pd-catalyst	Solvent	% Yield[b] 3a	4a
1	$Pd(PPh_3)_4$	EtOH	63	20
2	$Pd(PPh_3)_2Cl_2$	EtOH	58	40
3	10% Pd/C–PPh_3	EtOH	82	—
4	10% Pd/C	EtOH	42	20
5[c]	10% Pd/C–PPh_3	EtOH	—	—
6	PPh_3	EtOH	trace	40
7	10% Pd/C–PPh_3	1,4-dioxane	nd	60
8	10% Pd/C–PPh_3	THF	nd	27
9	10% Pd/C–PPh_3	CH_3CN	nd	36
10	10% Pd/C–PPh_3	Toluene	nd	48
11	10% Pd/C–PPh_3	DMF	nd	60

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (1.0 equiv.), 10% Pd/C or other Pd-catalyst (0.03 equiv.), PPh_3 (0.12 equiv.), CuI (0.06 equiv.), Et_3N (2 equiv.) at 80 °C for 12 h under N_2. [b] Isolated yield. [c] The reaction was carried out without CuI. nd = not detected.

[a]*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*
[b]*Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500049, India*
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds (Table 2) and crystallographic data for **3j**. See DOI: 10.1039/b617823e
‡ DRL publication number 634.

Table 2 Pd/C-mediated synthesis of 1(2*H*)-isoquinolones[a]

Entry	Haloenone	Alkyne	Product		% Yield[b]
1	 **1a**	 **2a**		**3a**	82
2	**1a**	 **2b**		**3b**	85
3	**1a**	 **2c**		**3c**	60
4	**1a**	 **2d**		**3d**	82
5	**1a**	 **2e**		**3e**	55
6	**1a**	 **2f**		**3f**	44
7	**1a**	 **2g**		**3g**	73
8	**1a**	 **2h**		**3h**	56
9	 **1b**	**2d**		**3i**	78
10	**1b**	**2g**		**3j**	65
11	**1b**	**2f**		**3k**	85
12	**1b**	**2b**		**3l**	84
13	**1a**	 **2i**		**3m**	43[c]
14	**1a**	 **2j**		**3n**	40[d]

[a] Reaction conditions: **1** (1.0 equiv.), **2** (1.0 equiv.), 10% Pd/C (0.03 equiv.), PPh_3 (0.12 equiv.), CuI (0.06 equiv.), Et_3N (2 equiv.) in EtOH at 80 °C for 12 h under N_2. [b] Isolated yield. [c] 3-Phenyl-4-phenylethynyl-2*H*-isoquinolin-1-one was isolated as a side product. [d] 3-*p*-Tolyl-4-tolylethynyl-2*H*-isoquinolin-1-one was isolated as a side product.

appeared at 1736 cm^{-1} for six-membered ring product **3a** and at 1786 cm^{-1} for five-membered ring product **4a**.

We were pleased to find that tandem C–C coupling–Schmidt reaction under Pd/C–Cu catalysis provided isoquinolones with a variety of substitution patterns (Table 2). The reaction proceeded well with a variety of terminal alkynes to give

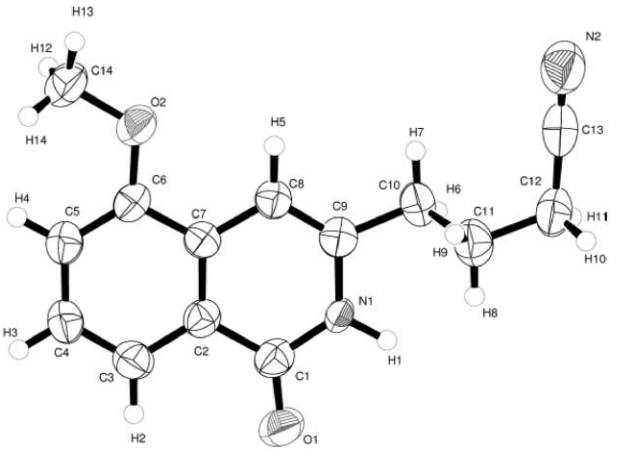
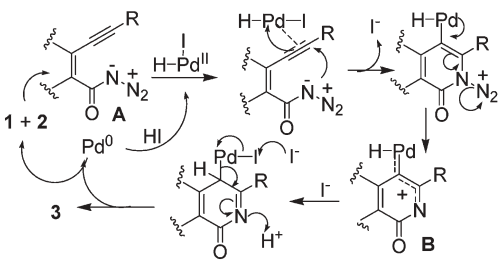


Fig. 1 X-ray crystal structure of **3j** (ORTEP diagram). Displacement ellipsoids are drawn at 50% probability level for non-hydrogen atoms.

3-substituted-1(2*H*)-isoquinolone **3** in good yields and isomeric products such as isoindolinones were not detected (entries 1–12, Table 2). The preparation of **3a** is representative: A mixture of 2-iodobenzoyl azide (0.3 g, 1.09 mmol), 10% Pd/C (0.034 g, 0.033 mmol), PPh_3 (0.034 g, 0.13 mmol), CuI (0.013 g, 0.065 mmol) and triethylamine (0.22 g, 0.3 mL, 2.17 mmol) in ethanol (10 mL) was stirred at 25 °C for 30 min under nitrogen. To this mixture was added 2-methylbut-3-yn-2-ol (0.092 g, 1.09 mmol) slowly with stirring. The reaction mixture was then stirred at 80 °C for 12 h, cooled to room temperature, diluted with EtOAc (50 mL) and filtered through Celite. The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether–EtOAc) to afford **3a** in 82% yield. The use of aryl alkynes afforded the desired products in low yield along with other side products (entries 13–14, Table 2). Notably, dimerization (homocoupling)[8] of the terminal alkynes was observed as a side reaction in a few cases especially when arylalkynes were used (entries 13–14, Table 2). Perhaps this was facilitated in the presence of Pd(II)[8d] generated *in situ* (see later for mechanistic discussion). All the isoquinolones synthesized were characterized by spectral[9] and analytical data and this was supported by the molecular structure of **3j** being confirmed by X-ray analysis (Fig. 1).§[10]

A possible mechanism involving *in situ* generation of *o*-alkynyl azido benzene **A** *via* Pd/C-mediated Sonogashira coupling followed by intramolecular acetylenic Schmidt reaction is shown in Scheme 2. Presumably, Pd(II) generated[11a] from Pd(0) activates the C–C triple bond[11b] which undergoes nucleophilic addition by the proximal nitrogen of the azide. Subsequent loss of dinitrogen



Scheme 2 Possible mechanism for the formation of isoquinolone.

produces the cationic intermediate **B**[7a] (stabilized by the electron donation from palladium), which as a result of hydride shift followed by the regeneration of Pd(0) finally affords the isoquinolone **3**. A mechanism involving generation of a nitrene-like intermediate,[7b] although it cannot be fully ruled out, would lead to the formation of a related product as a result of Curtius rearrangement.[11c] Also the observation that *o*-alkynyl benzamide is unreactive under the conditions studied (*i.e.* Pd/C–PPh_3–CuI or PPh_3–CuI at 80 °C for 24 h) disfavours the intermediacy of this amide that may be generated *in situ*. Nevertheless, a pathway similar to that shown in Scheme 2 can also be proposed for the formation of isoindolinone where nucleophilic addition of the azide to the C–C triple bond followed by the loss of dinitrogen produces the cationic intermediate corresponding to the five-membered ring product.[12]

In summary, we have developed a simple method to afford 3-substituted 1(2*H*)-isoquinolones that are not easily available from the previously known methodologies. The use of Pd/C–Cu catalysis is the key of this new transformation. This mild process was found to be general and highly regioselective, affording an array of compounds of potential biological significance.[13,14]

We thank Dr R. Rajagopalan and Prof. J. Iqbal for their encouragement and analytical group for spectral data. We also thank Mr P. Annamalai for biological assays.

Notes and references

§ CCDC 630060. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617823e

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9 Spectral data for selected compounds: **3a**; brown solid; mp 88–90 °C; ν_{max} (KBr)/cm^{-1} 3284 and 1736; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.60 (6 H, s, 2 × Me), 1.91 (1 H, br s, OH), 6.62 (1 H, s, CH=C), 7.43 (1 H, d, *J* 6.8 Hz, ArH), 7.47 (1 H, t, *J* 6.8 Hz, ArH), 7.70 (1 H, t, *J* 7.5 Hz, ArH) and 8.27 (1 H, d, *J* 7.5 Hz, ArH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 28.2 (2C), 83.9, 99.9, 125.9, 126.4, 128.1, 129.5, 131.9, 134.9, 137.2 and 161.7; *m*/*z* (CI Mass) 205 (M + 1, 100%), 187 (M^+ − 18, 30%); **3g**; brown solid; mp 54–56 °C; ν_{max} (KBr)/cm^{-1} 3423, 2243 and 1723; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.14–2.07 (2 H, m, CH_2), 2.51–2.42 (2 H, m, CH_2), 2.72 (2 H, t, *J* 7.2 Hz), 6.36 (1 H, s, CH=C), 7.38 (1 H, d, *J* 7.8 Hz, ArH), 7.49 (1 H, t, *J* 7.8 Hz, ArH), 7.70 (1 H, t, *J* 7.3 Hz, ArH), 8.26 (1 H, d, *J* 7.3 Hz, ArH); δ_C (50 MHz; $CDCl_3$; Me_4Si) 16.3, 22.6, 32.1, 104.4, 120.2, 125.3, 128.1, 129.5 (2C), 134.9 (2C), 136.9 and 162.5; *m*/*z* (CI Mass) 214 (M + 1,100%).

10 Crystallographic data for **3j**: single crystal from methanol, $C_{14}H_{14}N_2O_2$, M = 242.28, orthorhombic, space group $Pca2_1$, a = 23.78(1) Å, b = 4.560(3) Å, c = 11.134(7) Å, V = 1207(1) $Å^3$ and Z = 4, ρ_{calc} = 1.333 Mg m^{-3}, T = 298 K, μ = 0.907 cm^{-1}, 13936 processed reflections, 1401 unique reflections, R_{int} = 3.47% and final R factor = 0.067 (all data).

11 (*a*) B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1996, **118**, 6305. For activation of triple bond by HPdX, see: (*b*) C. H. Oh, C. Y. Rhim, H. H. Jung and S. H. Jung, *Bull. Korean Chem. Soc.*, 1999, **20**, 643; (*c*) See for example, N. Briet, M. H. Brookes, R. J. Davenport, F. C. A. Galvin, P. J. Gilbert, S. R. Mack and V. Sabin, *Tetrahedron*, 2002, **58**, 5761.

12 In an alternative mechanism, intermediate **A** adds HPdI to generate two vinyl palladium intermediates. Intramolecular azide addition to the double bond generates two triazines. Loss of nitrogen results in two aziridines. The aziridines then open to give vinyl palladium intermediates corresponding to the five- and six-membered ring products that finally afford **3** and **4** in the presence of triethylamine (which perhaps acts as a reducing agent). For intramolecular cycloaddition of an azide across a double bond leading to an aziridine, see: A. Padwa, A. Ku, H. Ku and A. Mazzu, *J. Org. Chem.*, 1978, **43**, 66 and G. Broggini, L. Garanti, G. Molteni and T. Pilati, *Tetrahedron: Asymmetry*, 2001, **12**, 1201.

13 Compound **3f** showed anticancer activity with an average GI_{50} of 28.32 on a tested panel of cancer cell lines [*e.g.* HT29 (colon), H460 (lung), LoVo (colon)] (see Electronic Supplementary Information).

14 For *in vitro* antitumour activity of compounds **3m–n** against various cell lines, see: W.-J. Cho, M.-J. Park, B.-H. Chung and C.-O. Lee, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 41.

