Cross-coupling of copper arylacetylides with *N*-(*o*-iodoaryl)hydrazines as a new method of synthesising 2-substituted indoles

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A new method is proposed for synthesising 2-substituted indoles by cross-coupling of copper(I) arylacetylides with *N*-(*o*-iodophenyl)hydrazines in DMF.

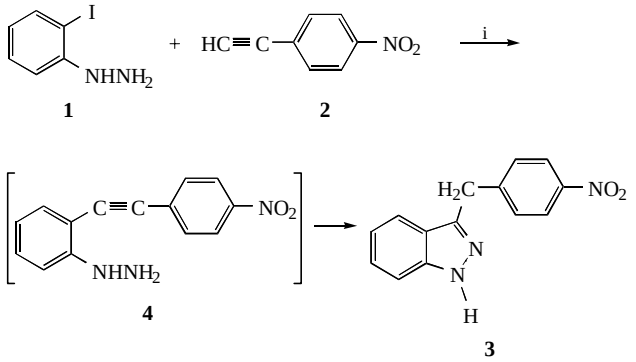
We have already reported on the cyclocondensation of activated *o*-chloroarylacetylenes with hydrazine which results in substituted indazoles.[1] This method is, however, limited by the necessity of using both aryl halides and acetylenic components which possess only electron-withdrawing substituents.

In addition, the cyclocondensation of *o*-chloro-substituted arylacetylenes with $NH_2NH_2 \cdot H_2O$ fails to give the intermediate compounds, *N*-(*o*-acetylenylaryl)hydrazines (substitution of a chlorine atom by a hydrazine group is the rate determining stage). Thus, it is impossible to study the cyclization of intermediates in a 'pure form' depending on the experimental conditions. It is also known that the direction of cyclization of (*o*-acetylenylaryl)carboxylic acid hydrazides, also containing two nitrogen atoms of differing nucleophilicity, may be controlled by varying the reaction conditions.[2]

We assume that an alternative way of synthesising *N*-(*o*-acetylenylaryl)hydrazines by interaction of *N*-(*o*-iodoaryl)hydrazines with either terminal acetylenes or their acetylide allows us not only to isolate intermediates but also to study the direction of *N*-(*o*-arylethynyl)hydrazine cyclization in the absence of acceptor substituents or even in the presence of donors. This, in turn, would make it possible to determine more precisely the influence of both internal (character of substituents) and external (conditions of cyclization) factors on the route of cyclization, its generality and limitations, and to synthesise other condensed heterocyclic systems.

The interaction between *N*-(*o*-iodophenyl)hydrazine **1** and *p*-nitrophenylacetylene **2** under standard cross-coupling conditions (Scheme 1) gives rise to 3-substituted indazole **3** in 38% yield. We have failed to isolate the expected intermediate **4**. Using chloride (**1**·HCl) as a more stable substrate, we managed to increase the yield of **3**† to 43%.

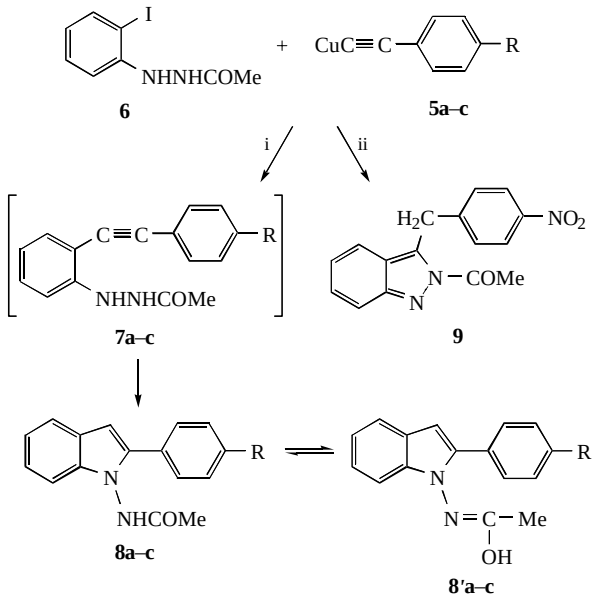
All attempts to condense **1** with *p*-methoxyphenylacetylene failed, since the reaction was followed by resinification. These results and the comparatively low yield of **3** are attributed to



Scheme 1 *Reagents and conditions*: i, N_2, $Pd(PPh_3)_2Cl_2$–CuI, Et_3N, 80 °C, 4.5 h.

† All compounds synthesised have satisfactory analytical and spectral data.

3: mp 117–118 °C (from benzene–hexane); ^{1}H NMR ($CDCl_3$) δ: 4.45 (s, 2H, CH_2), 7.0–8.2 (m, 8H, arom. H), 10.6 (br. s, 1H, NH); IR ($CHCl_3$, ν/cm^{-1}): 1350 and 1530 (NO_2), 3480 (br., NH).



Scheme 2 *Reagents and conditions*: i, N_2, DMF, 155 °C, 3–7 h; ii, N_2, Py, 110 °C, 3.5 h.

both the lability of initial iodohydrazine **1** and the low reactivity of halide atom due to the +M-effect of the hydrazine group. A similar result was observed for the reaction of arylacetylenes with vicinal iodoaminopyrazoles. To avoid complications, the authors used acylic protection of the amino group and replaced the catalytic variant of cross-coupling by the acetylide method of synthesis.[3]

We used this method in the present work. The acetylation of hydrazine **1** does indeed cause substrate stabilization and makes it possible to carry out cross-coupling of copper(I) *p*-nitrophenyl- **5a**, phenyl- **5b** and even of *p*-methoxyphenyl-acetylide **5c** with α-*N*-(*o*-iodophenyl)-β-*N*-(acetyl)hydrazine **6** (Scheme 2, Table 1).

However, we failed to isolate intermediates **7a–c** upon condensation. The reaction leads to the 2-substituted indoles **8a–c**‡ (30–75%). As expected, the reaction with **5a** proceeds most smoothly. It is interesting that compounds **8a–c** exist in a tautomeric equilibrium **8a–c** ⇄ **8′a–c** in solution (see NMR spectra).

The formation of the pyrrole rather than the pyrazole ring is related to the greater nucleophilicity of the amine nitrogen atom as compared with the amide nitrogen.

The application of pyridine as a solvent in the reaction of iodide **6** with **5a** changes the route of cyclocondensation. The

Table 1 Cyclocondensation of copper arylacetylides CuC≡C–C_6H_4–R-*p* with α-*N*-(*o*-iodophenyl)-β-*N*-(acetyl)hydrazine **6**.

Acetylide **5**	R	Indole **8**	DMF, 155 °C	Yield (%)
a	NO_2	**a**	3 h	74.7
b	H	**b**	5 h	32.0
c	OMe	**c**	7 h	41.0

formation of isoindazole **9**§ (30%) is probably related to the generation of a stronger N-anion nucleophile from the 'acidic' MeCONH group in the presence of base (Py).

All our attempts to carry out condensation of iodohydrazine **6** with copper(I) acetylide **5c** under similar conditions (Py) failed, probably due to the opposing polarization of a triple bond in intermediate **7c** (compared to **7a**) and due to the impossibility of forming an aromatic system.

We have managed to synthesize intermediate **7a** from **6** and **2** by using a catalytic variant of cross-coupling and decreasing the temperature to 80 °C. The yield of **7a**¶ reached 68%.

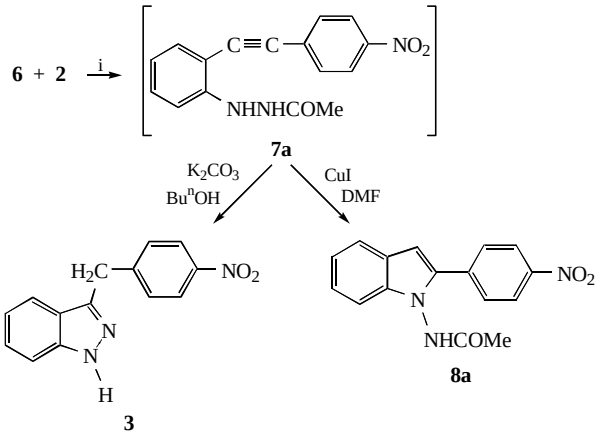
The interaction between iodide **6** and *p*-methoxyphenylacetylene under similar conditions fails to give the corresponding product **7c** (the reaction mass still contains initial **6**) and the reaction is accompanied by strong resinification. We assume that this is caused by the lower CH-acidity of *p*-methoxyphenylacetylene compared to that of *p*-nitrophenylacetylene.[4]

In attempting to remove the acylic protection in **7a** by boiling in *n*-butanol in the presence of K_2CO_3 we failed to isolate the expected intermediate **4** because the reaction was followed by cyclization into indazole **3** (48%).

We therefore suggest the direction of heterocyclization to be different in the absence of the base because the amine nitrogen atom is a stronger nucleophile than the amide one. Indeed, heating of **7a** in DMF in the presence of CuI at 120 °C gives indole **8a** in 75% yield (Scheme 3).

Thus, we have demonstrated the possibility of cross-coupling 1-alkynes and their acetylides with *N*-(*o*-iodophenyl)hydrazine and α-*N*-(*o*-iodophenyl)-β-*N*-(acetyl)hydrazine to produce condensed heterocyclic systems in a one-pot reaction:

1. The condensation of α-*N*-(*o*-iodophenyl)-β-*N*-(acetyl)-hydrazine with substituted copper(I) arylacetylides in DMF proceeds with the formation of a pyrrole ring and leads to the corresponding indoles. This is a new method for synthesising 2-substituted indoles. The same compounds are obtained by the cyclization of α-*N*-[(*o*-arylacetylenyl)phenyl]-β-*N*-(acetyl)-hydrazine in DMF in the presense of CuI.



Scheme 3 *Reagents and conditions*: i, N_2, $Pd(PPh_3)_2Cl_2$–CuI, Et_3N, 80 °C, 4.5 h.

2. The cyclocondensation of α-*N*-(*o*-iodophenyl)-β-*N*-(acetyl)-hydrazine with copper(I) acetylides with electron-withdrawing substituents gives 3-substituted isoindazoles under the effect of bases.

3. The Pd–Cu-catalysed cross-coupling of *N*-(*o*-iodophenyl)hydrazine with 1-alkynes bearing electron-withdrawing substituents in the presence of base is followed by cyclization to 3-substituted indazoles.

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‡ **8a**: mp 287.5–288 °C (from EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.52 and 2.22 [s, 3H, =C(OH)CH_3 and $COCH_3$], 6.83 and 6.95 (s, 1H, H-3 and H-3′), 7.2–8.45 (m, 8H, arom. H); IR ($CHCl_3$, ν/cm^{-1}): 1340 and 1510 (NO_2), 1680 (C=O), 3200, 3380 (br., NH, OH).

8b: mp 216–217 °C (from EtOAc); ^{1}H NMR ($CDCl_3$) δ: 1.55 and 2.10 [s, 3H, =C(OH)CH_3 and $COCH_3$], 6.65 and 6.75 (s, 1H, H-3 and H-3′), 7.10–8.25 (m, 9H, arom. H); IR ($CHCl_3$, ν/cm^{-1}): 1710 (C=O), 3230, 3400 (br., NH, OH).

8c: mp 193–194 °C (from EtOAc); ^{1}H NMR ($CDCl_3$) δ: 1.53 and 2.12 [s, 3H, =C(OH)CH_3 and $COCH_3$], 3.83 and 3.85 (s, 3H, OCH_3 and OCH_3'), 6.55 and 6.65 (s, 1H, H-3 and H-3′), 6.9–8.1 (m, 8H, arom. H); IR ($CHCl_3$, ν/cm^{-1}): 1040 (OCH_3), 1705 (C=O), 3250, 3390 (br., NH, OH).

§ **9**: mp 123–125 °C (from EtOAc); ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, 3H, CH_3), 4.41 (s, 2H, CH_2), 7.3–7.6 [m, 5H, H(β,β′,4,5,6)], 8.17 [d, 2H, H(α,α′), J 11.25 Hz], 8.46 (d, 1H, H-7, J 8.4 Hz); IR ($CHCl_3$ ν/cm^{-1}): 1350 (and 1330) and 1530 (NO_2), 1720 (and 1710) (C=O).

¶ **7a**: mp 165–166 °C (from EtOH–benzene); ^{1}H NMR ($CDCl_3$) δ: 2.15 (s, 3H, CH_3), 6.8–7.62 (m, 6H, H-2,3,4,5,2′,6′), 8.20 (d, 2H, H-3′,5′, J 8.6 Hz); IR ($CHCl_3$, ν/cm^{-1}): 1350 and 1530 (NO_2), 1710 (C=O), 2220 (C≡C), 3450 (br., NH).