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Efficient Preparation of the Isoindoline Framework *via* a Six Component, Tandem Double A^3-Coupling and [2+2+2] Cycloaddition Reaction

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Dedicated to the memory of Prof. Yoshihiko Ito of Kyoto University.

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Abstract: The preparation of tetrasubstituted isoindolines from three alkyne units, two aldehyde units and a primary amine *via* three consecutive reactions, two aldehyde-amine-alkyne couplings (A^3-couplings) and a final [2+2+2]cycloaddition, in a single synthetic operation, is described. The A^3-couplings are catalyzed by copper bromide and the cycloaddition is catalyzed by Wilkinson's catalyst. It was found that many catalysts known to be efficient at the cycloaddition step were not suitable when this step was part of the tandem reaction sequence. Wilkinson's catalyst was found to be unique in its suitability for the overall domino reaction sequence.

Keywords: alkynylation; copper; cycloaddition reaction; domino reaction; multicomponent reaction; rhodium

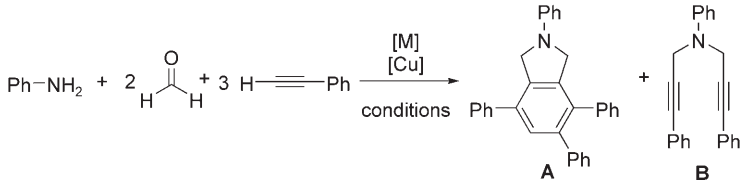
Tandem/cascade/domino reaction processes have received a good deal of attention over the last decade due to the efficiency and step-economy inherent in the methodology.[1] The hallmark of tandem reactions is a considerable increase in molecular complexity resulting from a single synthetic step.[1] The conversion of primary amines, aldehydes, and alkynes to isoindolines in a single synthetic operation is without precedent. This methodology has potential for application to the efficient and economical preparation of compounds with industrial and pharmaceutical importance.

The ability of an isoindoline to act as a diuretic 100 times more active than chlorothiazide was reported over four decades ago.[2] The first anti-tumour activity for an isoindoline was discovered nearly three decades ago.[3] In the decades to follow so many reports of various biological activities of isoindolines emerged that a comprehensive summary is not possible in this communication. The most recent reports show herbicidal activity,[4] dipeptidyl peptidase inhibition,[5] antagonism of the 5-HT_{2C} receptor,[6] treatment of cutaneous lupus,[7] metabotropic glutamate receptor potentiator activity,[8] and treatment of cancer,[9] or abnormal cell growth.[10] Reports of the use of isoindolines as key components of pigment compositions also continue to emerge.[11] Isoindolines have been recently shown to be active ingredients in the natural commercial drug ant lion.[12] Isoindolines have also found use as novel spin probes useful for studying cancer.[13] A number of the active isoindoline derivatives mentioned have 1- and/or 3-oxo substituents which can be readily prepared by oxidation of the benzylic positions.[14]

Besides being efficient and economical, this methodology could be useful for expanding the repertoire of known useful isoindoline derivatives. The isoindoline preparation described herein would be suitable for combinatorial chemistry, using a library of various substitutions on aromatic alkynes and amines. Previously reported preparations of isoindolines begin with a relatively complex starting material. Either the aromatic ring is already in place and needs to have appropriately placed functional groups to construct the dihydropyrrole skeleton of the isoindoline,[15] or a dipropargylamine is used as the starting material.[16] The second example of synthesizing isoindolines by [2+2+2]cycloaddition starting with dipropargylamines has been limited largely to tosylamines.[16] This is because the methodology for synthesizing those dipropargylamines requires a highly electron-deficient amine.[17]

Recently we reported a tandem double direct alkynylation of primary followed by secondary imines formed *in situ* (double A^3-coupling) to generate di-

Table 1. Screening of catalysts for tandem, one-pot double A^3-coupling and [2+2+2]cycloaddition using aniline as primary amine.[a]



Entry	CuBr[b] [mol%]	[M] [mol%]	T [°C]	Time [h]	Solvent	Yield[c]**A** [%]	Yield[c]**B** [%9
1	30	none	40–80	8	Neat	0	81
2	None	$RhCl(PPh_3)_3$ (3)	40–80	8	Neat	0	0
3	15	$RhCl(PPh_3)_3$ (3)	40–80	8	Neat	39	23
4	30	$RhCl(PPh_3)_3$ (5)	60	17	Neat	53	3
5	30	$RhCl(PPh_3)_3$ (3)	60	18	Neat	47	17
6	30	$RhCl(PPh_3)_3$ (1)	60	26	Neat	29	47
7[d]	30	$RhCl(PPh_3)_3$ (3)	40–80	8	Neat	76	5
8[f]	30	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)	24–80	9	H_2O:MeOH, 9:1	0	78
9[e]	30	$Ru_2Cl_4(C_{10}H_{16})_2$ (2.5)	24–80	9	H_2O:MeOH, 9:1	0	66
10[f]	30	$RuCl_2(PPh_3)_3$ (5)	57	25	Toluene	0	73
11	15	Cp*RuCl(cod) (5)	55	19	Toluene	0	51
12	3	$CpCo(CO)_2$ (6)	27–100	21	Toluene	0	0
13	15	$Ni(cod)_2$ (5)/PPh_3 (20)	60	21	THF	0	0

[a] Reaction scale varied from 0.2–0.6 mmol aniline, but always 3 equivs. formaldehyde (37 wt% in H_2O) and 5 equivs. phenylacetylene. Neat reactions were run with 9 equivs. phenylacetylene. All reactions were degassed and run under inert atmosphere.

[b] CuCl, CuI, and CuOTf gave inferior yields.

[c] Yields determined by integrating methylene protons using 400 MHz ^{1}H NMR and mesitylene as quantitative internal standard.

[d] See Supporting Information for detailed screening of various conditions using Wilkinson's catalyst.

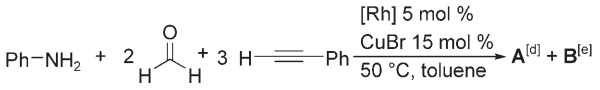
[e] Catalyst was dichlorobis(μ-chloro)bis[(1,2,3,6,7,8-η)-2,7-dimethyl-2,6-octadien-1,8-diyl]diruthenium(IV) CAS: [34801-97-3].

[f] Increasing the temperature to 100 °C for over 40 h will produce up to a 1:1 ratio of **A**:**B** but results in significant degradation of **A** even under N_2.

propargylamines from a wide variety of aliphatic or aromatic primary amines and aliphatic or aromatic alkynes.[18] This methodology complements the scope of dipropargylamines that are readily available. While working on this we envisioned adding an appropriate catalyst for a [2+2+2]cycloaddition so the dipropargylamines required for the isoindoline synthesis could be generated *in situ* and then react immediately to form the isoindoline in the same pot. Ruthenium, cobalt, rhodium, and nickel are the most common transition metals used to catalyze [2+2+2]cycloadditions.[19] Wilkinson's catalyst is well known for being efficient at catalyzing intermolecular [2+2+2]cycloadditions between 1,6-diynes, including dipropargylamines, and monoalkynes.[20]

From Table 1, entries 1 and 2 it is apparent that copper bromide[21] alone is sufficient to generate the dipropargylamine in good yield under the conditions used, whereas Wilkinson's catalyst does not catalyze the A^3-couplings. However, Wilkinson's catalyst seems to interfere with the initial A^3-couplings since the overall yield of dipropargylamine and isoindoline increases with decreased loading of Wilkinson's catalyst, although this also causes lower conversion of dipropargylamine to isoindoline (Table 1, entries 4–6). Ruthenium is known to be an efficient co-catalyst with copper for A^3-couplings[22] and the complexes listed in Table 1, entries 9[23] and 11[24] are known to be excellent catalysts for [2+2+2]cycloadditions. For this reason we expected a ruthenium catalyst to be most suitable for the overall tandem reaction sequence. The highest expectations were for Cp*RuCl(cod) based on the literature examples that include electron-deficient and relatively electron-rich dipropargylamines,[24] yet this catalyst gave no trace of isoindoline even with a number of variations in reaction time, temperature, and solvent. As a control the corresponding dipropargylamines were isolated and then combined with Cp*RuCl(cod) again under identical conditions and isoindoline product was detected in moderate yield by NMR. From this we concluded that the catalyst is altered in the early stage of the cascade reaction processes in a way that renders it ineffective for the final cycloaddition. The ruthenium

Table 2. Screening of rhodium complexes for tandem, one-pot double A^3-coupling and [2+2+2]cycloaddition using aniline as primary amine.[a]



Entry	[Rh]	Time [h]	Yield[c] **A** [%]	Yield[c] **B** [%]
1	$Rh(PPh_3)_3Cl/AgBF_4$	23	6	0
2	$Rh(PPh_3)_3Cl//AgOTf$	22	14	0
3[b]	$[Rh(cod)Cl]_2/P(Me)_3$	18	0	45
4[b]	$Rh(cod)Cl]_2/P(Cy)_3$	26	0	34
5[b]	$Rh(PPh_3)_3Cl$	29	29	0
6	$Rh(cod)(PPh_3)_2PF_6$	40	3	0
7	$Rh(cod)_2BF_4$	41	14	21
8	$Rh(cod)_2BF_4/PPh_3$	21	21	13

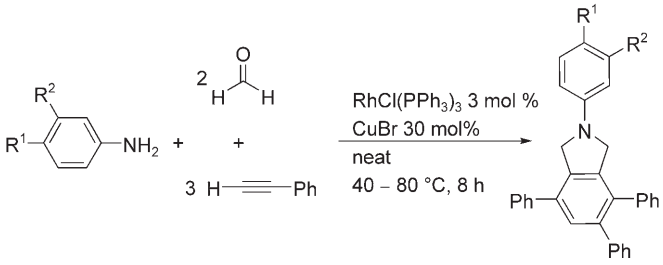
[a] Reaction scale was 0.4 mmol aniline, with 3 equivs. formaldehyde (37 wt% in H_2O) and 5 equivs. phenylacetylene in 0.25 mL solvent.
[b] Paraformaldehyde providing 3 equivs. of formaldehyde was used in place of the regular aqueous formadehyde solution and the reaction was carried out under anhydrous conditions.
[c] Yields determined by integrating methylene protons using 400 MHz ^1H NMR and mesitylene as quantitative internal standard.
[d] Isoindoline (see Table 1).
[e] Dipropargylamine (see Table 1).

triphenylphosphine and *p*-cymene complexes gave isoindoline in low yield under the cascade conditions only if the temperature was raised to over 100 °C for over 24 h and no isoindoline was observed with moderate temperature and time (Table 1, entries 8 and 10). The nickel[25] and cobalt[26] catalysts used are also quite common and well known for efficient [2+2+2]cycloadditions(Table 1, entries 12 and 13). However, copper-catalyzed A^3-couplings did not occur in their presence so that the potential for efficient cycloadditions under the tandem reaction conditions could not be evaluated.

Variations in counter ion and ligand were then explored for rhodium complexes (Table 2, entries 1–8). Electron-rich phosphine ligands rendered the rhodium complex incapable of catalyzing the cycloaddition reaction (Table 2, entries 3 and 4). Chlorine proved to be the best counter ion when compared to other commonly used counter ions for the cycloaddition step (Table 2, entries 1 and 2, 5–8) although all were capable of producing isoindoline under the tandem reaction conditions.

Clearly the most electron-rich amines gave the worst results (Table 3, entries 4 and 6). A methyl

Table 3. Tandem, one-pot double A^3-coupling and [2+2+2]cycloaddition for various primary amines.[a]



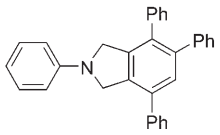
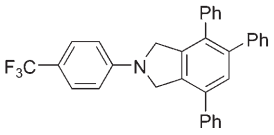
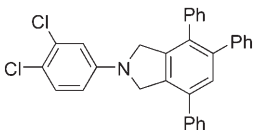
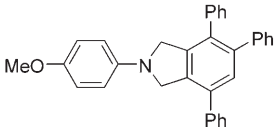
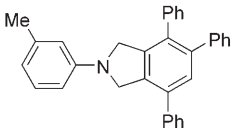
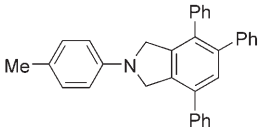
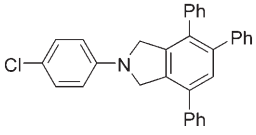
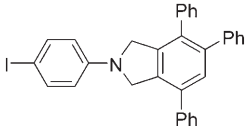
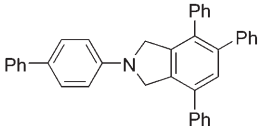
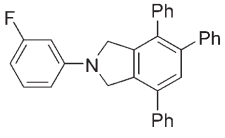
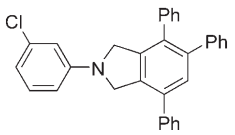
Entry	Product	Yield[b] [%]
1		78 (69)
2		62 (58)
3		66 (57)
4		33 (24)
5		60 (51)
6		15 (13)
7		86 (78)
8		85 (76)
9		76 (69)
10		84 (70)

Table 3. (Continued)

Entry	Product	Yield[b] [%]
11		72 (65)

[a] Reactions were run neat with 0.56 mmol primary amine, 3 equivs. formaldehyde (135 μL, 37 wt % in H_2O) and 9 equivs. phenylacetylene; Reaction mixture was degassed and agitated for 2 h at 40 °C and 6 h at 80 °C.

[b] Yields determined by integrating methylene protons using 400 MHz ^{1}H NMR and mesitylene as quantitative internal standard. Isolated yields after flash chromatography shown in parenthesis.

group in the *meta* position provides less inductive electron donation than either a methyl or a methoxy group in the *para* position, (Hammett substituent parameters of $\sigma = -0.06$, -0.14, and -0.12, respectively)[27], which could help to explain the difference between entries 5 and 6 in Table 3. Electron deficiency, on the other hand, impairs the A^3-couplings since highly electron-deficient amines such as tosylamines are incapable of undergoing this reaction. Thus, although there appears to be an advantage to electron-withdrawing substituents (Table 3, entries 1, 7, 8, 10 and 11) there is an upper limit as seen by the decrease in yield when *p*-trifluoromethane or two chloro substituents are present (Table 3, entries 2 and 3). When either aliphatic alkynes or amines were used under the optimal conditions (Table 3) isoindoline could be detected by mass spectroscopy, but conversion was too low to isolate the product.

This methodology provides a convenient, efficient, and economical way to screen new isoindolines which have enormous potential for industrial application. Further work to overcome the limitations with aliphatic substrates is ongoing.

Experimental Section

Typical Procedure for the Tandem Double A^3-Coupling and [2+2+2] Cycloaddition Reaction

Copper bromide and Wilkinson's catalyst were combined in a screw cap tube open to air. Phenylacetylene, formaldehyde solution (37 wt % in water), and primary amine were then added in that order in open air *via* syringe. Solid amines were also added last for consistency. The tube was then sealed with a cap fitted with a valve connected to a Schlenk line and after a five minute initial stir the reaction mixture was degassed by freeze-pump-thaw three times using liquid nitrogen and then left with an overpressure of nitrogen gas at 40 °C for 6 h. After 6 h the temperature was increased to 80 °C for two additional hours and then the reaction mixture was filtered open to air through ~1–2 cm of silica with ethyl acetate. Ethyl acetate was removed with rotary evaporation followed by high vacuum for 1 h before dissolving in 1 mL of $CDCl_3$ for NMR analysis of the crude reaction mixture.

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