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Copper catalysed domino decarboxylative cross coupling-cyclisation reactions: synthesis of 2-arylindoles

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ABSTRACT

The efficient synthesis of 2-arylindoles and 6*H*-isoindolo[2,1-*a*]indol-6-one through copper catalysed domino sp-sp^2 decarboxylative cross-coupling and subsequent cyclisation reactions of arylpropiolic acids with 2-iodotrifluoroacetanilide has been described. This methodology also demonstrates that indolo-[1,2-*c*]quinazolin-6(5*H*)-one can be obtained with the elimination of trifluoromethyl anion.

Heterocyclic compounds, particularly indole, occur widely in nature as partial structure of many alkaloids and have unique biological activities.[1] 2-Arylindole moiety has been found in many biologically active molecules.[2] Cycloisomerisation reaction of 2-alkynylanilines using transition metal catalyst[3] or Lewis acid[4] or strong base[5] was one of the efficient methodologies for the synthesis of 2-substituted indoles. Recently, Liu and Ma[6] and Shen and co-workers[7] have independently synthesised the 2-substituted indoles from protected 2-haloanilines and terminal alkynes using cuprous iodide as the catalyst. Recently, decarboxylative couplings have been found to be successful as one of the C–C bond construction process. The carboxyl group functionalised alkynes are easy to handle, simple to store, have relatively high boiling point, and therefore might serve as an alternative to terminal alkynes, which are difficult to handle (e.g., methylacetylene with low boiling point of −23 °C). Carboxylate groups can effectively function as a leaving group in cross-coupling, in which carbon dioxide is produced as the by-product.[8] Though palladium catalysed decarboxylative coupling reactions are well known, the copper-only-mediated reactions are not very popular. A catalytic domino sequence would be the attractive method towards developing efficient protocols that minimise the requisite reagents, solvents, time, separation processes, cost for the desired transformation and the formation of waste.[9] To the best of our knowledge, there are no reports describing the decarboxylative coupling to access 2-substituted indole related skeleton. Inspired by this a decarboxylative route for preparing 2-substituted indole has been developed and the observed interesting results are presented in this Letter.

Cuprous chloride catalysed decarboxylation of propiolic acids has been recently reported[10] and cuprous iodide/amino acid catalytic system has been used in the cross coupling of aryl and vinyl halides with various nucleophiles.[11] We hypothesised that the decarboxylative cross coupling and cyclisation of alkynyl carboxylic acids with 2-iodotrifluoroacetanilide could be achieved using a copper/amino acid catalytic system under proper conditions. Initially the coupling of 2-iodotrifluoroacetanilide (**1a**) with phenyl propiolic acid (**2a**) has been studied as a model reaction (Table 1). Liu and Ma[6] have found this trifluoroacetyl system is quite suitable for this type of reactions and hence **1a** has been chosen for the present work. No product was obtained, when the reaction was performed with (i) cuprous iodide (5 mol %) with L-proline (15 mol %)/potassium carbonate (2 equiv) at 60 °C and (ii) cuprous iodide (5 mol %) with L-proline (15 mol %)/Et_3N (2 equiv) at 80 °C in DMF (Table 1, entries 1 & 2). However, the expected product, 2-phenylindole (**3a**), was obtained in 58% yield when tetra *n*-butylammonium fluoride (2 equiv) was used as the base (Table 1, entry 3) whereas 65% of **3a** was obtained when potassium carbonate was used as the base (Table 1, entry 4). Among the catalysts tested, all copper(I) salts such as CuI, CuCl, CuBr and CuCN showed catalytic activities (Table 1, entries 4–7). Cuprous bromide was found to be the best catalyst among the copper salts. The α-amino acid based ligands were then optimised to improve the yield of **3a** (Table 1, entries 8–10) and L-proline gave better yield. This optimised condition consumed long reaction time (about 15 h) and gave moderate yield (75%) (Table 1, entry 6). To minimise

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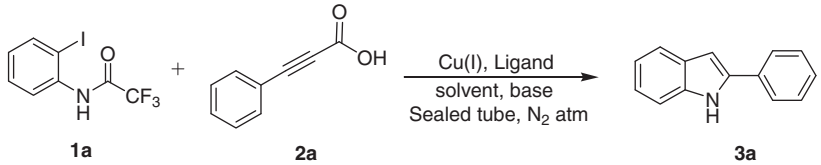
Table 1
Optimisation of reaction condition[a]



1a 2a 3a

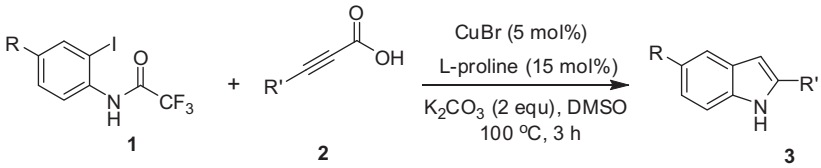
Entry	Cu(I) (5 mol %)	Ligand (15 mol %)	Base (2 equiv)	Solvent	*T* (°C)	Time (h)	Yield[b] (%)
1	CuI	L-Proline	K_2CO_3	DMF	60	24	N/R
2	CuI	L-Proline	Et_3N	DMF	80	24	N/R
3	CuI	L-Proline	TBAF·H_2O	DMF	80	15	58
4	CuI	L-Proline	K_2CO_3	DMF	80	15	65
5	CuCl	L-Proline	K_2CO_3	DMF	80	24	60
6	CuBr	L-Proline	K_2CO_3	DMF	80	15	75
7	CuCN	L-Proline	K_2CO_3	DMF	80	24	55
8	CuBr	*N*,*N*-Dimethyl glycine	K_2CO_3	DMF	80	24	64
9	CuBr	*N*-Methyl glycine	K_2CO_3	DMF	80	24	62
10	CuBr	L-4-Hydroxy proline	K_2CO_3	DMF	80	24	68
11	CuBr	L-Proline	K_2CO_3	DMF	100	7	76
12	CuBr	L-Proline	K_2CO_3	DMF	120	3	73
13	CuBr	L-Proline	K_2CO_3	DMF	120	0.5	75[c]
14	CuBr	L-Proline	K_2CO_3	DMSO	100	3	90
15	CuBr	L-Proline	K_2CO_3	DMA	100	7	63
16	CuBr	L-Proline	K_2CO_3	H_2O	100	24	N/R

[a] All of the reactions were carried out with substrate **1a** (5 mmol), **2a** (5 mmol), copper catalyst (5 mol %), ligand (15 mol %) and base (10 mmol) in the solvent (10 mL) under N_2 atmosphere in a sealed tube.
[b] Isolated yield.
[c] Microwave condition.

the reaction time, the reaction was conducted at higher temperature and also under microwave condition. The reaction got completed in 7 h at 100 °C and 3 h at 120 °C, but under the latter condition, the yield was slightly decreased (Table 1, entry 12) compared to the former one (Table 1, entry 11). When the reaction was carried out under microwave irradiation at 120 °C, 75% of **3a** was obtained requiring 30 min for complete conversion (Table 1, entry 13). DMSO was found superior to other solvents tested, which afforded excellent yield of **3a** at 100 °C in 3 h (Table 1, entry 14). The green solvent water was not effective in bringing out this transformation (Table 1, entry 16).

The scope of this methodology was extended to other arylpropiolic acids **2** and differently substituted 2-iodotrifluoroacetanilides, **1** (Table 2). Several methods are available for the synthesis of arylpropiolic acids **2** and the arylpropiolic acids employed in this investigation were prepared by Sonogashira reaction[12] at room

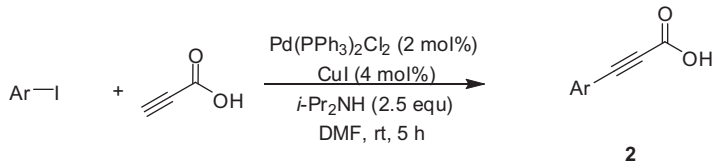
Table 2
Synthesis of 2-aryl substituted indoles[a]



1 2 3

Entry	Iodide **1**	Alkynoic acid **2**	Product **3**	Yield[b] (%)
1	R = H, **1a**	R′ = 3,4-Difluorophenyl, **2b**	**3b**	80
2	R = H, **1a**	R′ = 3-Fluoro-4-ethoxyphenyl, **2c**	**3c**	85
3	R = H, **1a**	R′ = 3-Bromophenyl, **2d**	**3d**	88
4	R = H, **1a**	R′ = 4-Bromophenyl, **2e**	**3e**	84
5	R = H, **1a**	R′ = 4-Chlorophenyl, **2f**	**3f**	90
6	R = H, **1a**	R′ = 2-Fluorophenyl, **2g**	**3g**	81
7	R = H, **1a**	R′ = 4-Carboxyphenyl, **2h**	**3h**	70
8	R = H, **1a**	R′ = 4-Methoxycarbonylphenyl, **2i**	**3i**	75
9	R = H, **1a**	R′ = 3-Methoxycarbonylphenyl, **2j**	**3j**	84
10	R = H, **1a**	R′ = 4-Nitrophenyl, **2k**	**3k**	79
11	R = H, **1a**	R′ = 2-Thienyl, **2l**	**3l**	71
12	R = $COOCH_3$, **1b**	R′ = Phenyl, **2a**	**3m**	76
13	R = CN, **1c**	R′ = Phenyl, **2a**	**3n**	78
14	R = Br, **1d**	R′ = Phenyl, **2a**	**3o**	86

[a] Reaction condition: alkynoic acid **2** (5 mmol), **1** (5 mmol), CuBr (5 mol %), L-proline (15 mol%) and K_2CO_3 (10 mmol) in DMSO (10 mL) at 100 °C for 3 h.
[b] Isolated yield.



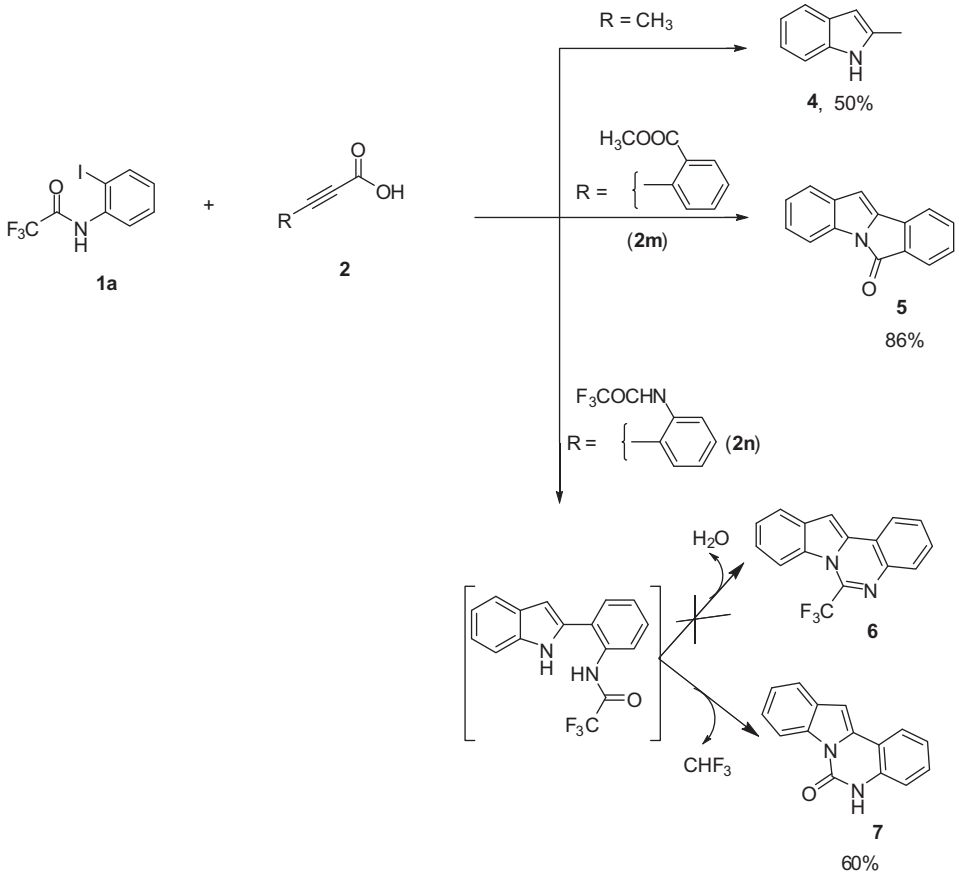
Ar = Phenyl/ 3,4-Difluorophenyl/ 3-Fluoro-4-ethoxyphenyl/ 3 or 4-Bromophenyl/ 2-Fluorophenyl/ 4-Carboxyphenyl/ 3 or 4-Methoxycarbonylphenyl/ 4-Nitrophenyl/ 2-Thienyl/ 2-Trifluoroacetamidophenyl

Scheme 1. Synthesis of arylpropiolic acids.

temperature. A reaction between aryl iodide and propiolic acid in the presence of $Pd(PPh_3)_2Cl_2$/CuI catalytic system afforded the required arylpropiolic acids (Scheme 1). As shown in Table 2, various alkynyl carboxylic acids and 2-iodotrifluoroacetanilide derivatives smoothly underwent sequential reactions to afford the desired product **3** in good to excellent yields.[13] Interestingly when arylpropiolic acid bearing the carboxyl group was subjected to the reaction, sp-decarboxylation is preferred over sp^2-decarboxylation (Table 2, entry 7). The heteroaryl alkynoic acid also undergoes this transformation in good yield (Table 2, entry 11). Reaction with alkylpropiolic acid, 2-butynoic acid, afforded moderate yield of the desired product **4** (Scheme 2). The corresponding alkyne, methylacetylene, may not undergo this transformation. In the case of 2-butynoic acid, copper acetylide formed after decarboxylation and undergo sequential reactions with stoichiometric amount of 2-butynoic acid.

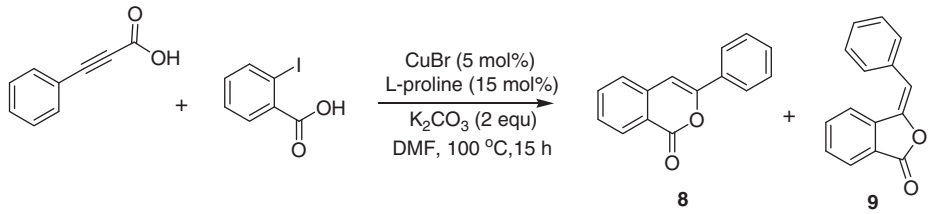
As shown in Table 2, the reaction between 2-iodotrifluoroacetanilide and 3-(4-(methoxycarbonyl)phenyl)propiolic acid or 3-(3-(methoxycarbonyl)phenyl)propiolic acid afforded the desired indole nucleus (Table 2, entries 8 & 9). However when the methoxycarbonyl group is at the *ortho* position of the phenyl ring, an isoindolone derivative, 6*H*-isoindolo[2,1-*a*]indol-6-one (**5**), was obtained in good yield (Scheme 2) through a sequential decarboxylative cross coupling–cycloisomerisation–cyclisation reactions. 6*H*-Isoindolo[2,1-*a*]indol-6-one is the core structure for a number of biologically active compounds[14] and it was also used as the intermediate for the synthesis of NorA efflux pump inhibitors.[2d,15]

This protocol was further applied to the reaction between 2-trifluoroacetamido phenyl propiolic acid and 2-iodotrifluoroacetanilide which afforded indolo[1,2-*c*]quinazolin-6(5*H*)-one **7** in 60% yield, instead of the expected quinazoline nucleus **6** through the elimination of water (Scheme 2). Interestingly, the elimination of



Reaction condition: CuBr (5 mol%), L-proline (15 mol%), K_2CO_3 (2 equ), DMSO, 100 °C, 5 h

Scheme 2. Reaction between 2-alkynoic acid and 2-iodotrifluoroacetanilide.



Scheme 3. Reaction between 2-iodobenzoic acid and phenylpropiolic acid.

trifluoromethyl anion (as fluoroform) has been noticed, which is a very rare phenomenon.[16] The structure of indolo[1,2-*c*]quinazolin-6(5*H*)-one **7** was confirmed by spectral data (ESI-MS, ^{1}H NMR, ^{13}C NMR and FT IR) and also matched with the previously reported.[17] Recently, Ma's group[18] have synthesised the 2-trifluoromethylindole and 2-trifluoromethylbenzimidazole derivatives from 2-iodotrifluoroacetanilide with ethyl acetoacetate and primary amine respectively using CuI/L-proline catalytic system, where no case of trifluoromethyl anion elimination has been reported.

When the reaction between 2-iodobenzoic acid and phenylpropiolic acid was effected under same condition, either **8** or **9** were not obtained. But when DMF was used as the solvent instead of DMSO, a mixture of isocoumarin **8** and phthalide **9** was obtained in equal amount with an overall yield of 52% (Scheme 3).

In summary, we have developed the methodology for the synthesis of 2-aryl indoles related skeleton starting from propiolic acid and aryl iodides. This conversion tolerates a wide range of functional groups which can be useful for further synthetic transformation. Additionally, the synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-one and [1,2-*c*]quinazolin-6(5*H*)-one has been achieved under the same condition. The described protocol is more convenient for the preparation of the target compounds in comparison with the literature methods[2–7] and good to excellent yields can be achieved using readily available starting materials.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 06. 023.

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13. *General procedure for the synthesis of **3**, **4**, **5**, **7**, **8** and **9**.* To a mixture of $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (4 mol %) and DMF (15 mL) taken in a flask, aryl iodide (10 mmol), propiolic acid (12 mmol) and diisopropylamine (25 mmol) were added in that sequence under nitrogen atmosphere. After stirring the reaction mixture at room temperature for 5 h, the resulting mixture was diluted with ethyl acetate, filtered through celite bed, the filtrate was washed with cold aqueous KOH solution (1 × 100 mL) and acidified with dilute sulfuric acid (10% solution) at 0 °C. The solid obtained was extracted with dichloromethane and the extract was washed with water, brine solution and dried over anhydrous sodium sulfate. The organic layer was concentrated in vacuo at 40 °C, dried to get the arylpropiolic acid. Arylpropiolic acid (5 mmol) or 2-butynoic acid (5 mmol) was transferred into a 30 mL glass tube and then iodo compound (5 mmol), L-proline (15 mol %), cuprous bromide (5 mol %) and potassium carbonate (10 mmol) in DMSO or DMF (10 mL) were added in that order. The sealed tube was then subjected to a vacuum and refilled with nitrogen for five times under stirring at room temperature. The tube was placed in an oil bath and heated with stirring at 100 °C for 3–5 h. After the reaction, the reaction mixture was mixed with ethyl acetate and washed with water, brine solution and dried over anhydrous sodium sulfate. Removal of the

solvent in vacuo and purification of the residue by silica-gel column chromatography with hexane/ethyl acetate afforded the desired product. See Supplementary data for spectral data of all compounds.

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