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Cu-HAP: An efficient and reusable additive free catalyst for the coupling of aryl bromides with 5, 5-dimethylhydantoin and synthesis of Nilutamide analogues

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Abstract: *Copper–Aluminium Hydroxyapatite (Cu-HAP) catalyst was effectively used in the C-N bond coupling of aryl bromides (**1a-h**) and 5, 5-dimethylhydantoin (**2**) without any ligand and base, to afford corresponding N-Alkylated aromatic amines **(3a-h)** in good yields. The catalyst was quantitatively recovered from reaction mixture by simple filtration and reused for four cycles with consistent activity.*

Key words*: Nilutamide · 5, 5-dimethylhydantoin · Copper–Aluminium Hydroxyapatite (Cu-HAP) · C-N coupling · Aryl bromides.*

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I. Introduction

N-alkyl and N-aryl dimethylhydantoins are common motifs in pharmaceutical research [1-2]. The key step in synthesis of these compounds is metal-mediated C-N cross coupling reactions between aryl bromides and hydantoin derivatives. The common methods for such type of reactions involve use of ligand assisted palladium and copper catalysts in presence of a base [3]. However these protocols require harsh conditions, also not useful in large scale industrial applications due to their high cost and toxicity.

The development of heterogeneous catalysts for the fine chemical and process development synthesis has become major area of research recently in pharmaceutical industry, as the potential advantages of these solid materials (simplified recovery and reusability) over homogeneous system can make a major impact on the environmental performance of synthesis [4]. Chowdary et.al reported hydroxyapatite-supported copper (Cu-HAP) [5] and Cu (II)-NaY [6] catalyzed coupling of aryl bromides with heterocyclic amines without use of additives. Very recently, Tan et.al repored Cobalt catalysed cross coupling of non aromatic amides with iodobenzene in water [7]. Although these results are encouraging, however there is considerable scope for improvement. For example in particularly, they are ineffective for alkylamines and electron donating aryl bromides. Therefore Cu-HAP catalysed C-N cross coupling reaction needs more efficient procedures to expand the scope of this methodology and to employ more substrates. We wish to first time report efficient Cu-HAP catalyzed N-Arylation of aryl bromides with 5,5-dimethylhydantoin under ligand and base free conditions.

Nilutamide [8], 5, 5-dimethyl-3-[4-nitro-3-trifluoromethyl) phenyl] imidazolidine-2, 4-done, is a nonsteroidal orally-active antiandrogen derivative-HAe that behaves as a competitive antagonist of the androgen receptors. This nitroaromatic compound is used in the treatment of advanced prostate cancer.

II. Results And Discussion

In our preliminary studies to find the best conditions for coupling reaction under ligand and base free conditions, we choose the coupling reaction of 4-bromo-1-nitro-2-(trifluoromethyl)benzene (**1a**) with 5,5-dimethylhydantoin (**2**) to give Nilutamide (**3a**) with a catalytic amount of Cu-HAP as a model reaction and some of the key results obtained are shown in Table 1. Initially we started the reaction with 5 mol % of Cu-HAP as heterogeneous catalyst and DMF as solvent which afforded poor yields of required product (Table 1, entry 1). An increase in the catalyst loading from 5 mol % to 20 mol % of Cu-HAP, resulted in an increase in the yield up to 88% (Table 1, entry 1-3). Further increases in catalyst loading had no profound effect on the yields of the desired product (Table 1, entry 4). Also the reaction was carried out at different temperature ranging from 90 ^{o}C to 130 ^{o}C and found that at 100-105 ^{o}C the yield of the reaction was 88 % in 8 h. Further increase in the temperature, does not affect the yield of the reaction (Table 1, entry1-5). Next we also screened different solvent system for the C-N coupling of **1a** with 5,5-dimethylhydantoin **(2)**, and it was observed that low boiling polar solvents such as ACN and 1, 4-dioxan were found to be ineffective with different concentrations of Cu-HAP

(Table 1, entry 6-11). Although *N*,*N*-dimethylformamide (DMF) was found to be effective (88%) with negligible amount of Cu leaching. Notably, the reaction did not proceed without Cu-HAP at 100^{o}C (Table 1, entry 12), indicating that Cu-HAP is crucial to this reaction. As a result, the reaction conditions described in Table 1, entry 3 were selected as the standard conditions for further investigations.

Table 1 Optimization for synthesis of Nilutamide using Cu-HAP

S No	Catalyst	mmol	Solvent	Temp. (^{o}C)	Time (h)	Yield[a] (%)
1	Cu-HAP	5	DMF	90	12	31
2	Cu-HAP	10	DMF	100	12	66
3	**Cu-HAP**	**20**	**DMF**	**100**	**8**	**88**
4	Cu-HAP	40	DMF	110	8	63
5	Cu-HAP	20	DMF	130	18	49
6	Cu-HAP	20	ACN	80	12	-
7	Cu-HAP	20	ACN/H_2O (1:1)	110	12	15
8	Cu-HAP	40	ACN/H_2O (1:1)	110	12	26
9	Cu-HAP	20	1, 4-Dioxan	100	12	33
10	Cu-HAP	40	1, 4-Dioxan	100	12	41
11	Cu-HAP	20	THF/ H_2O (1:1)	100	12	22
12	-	-	DMF	100	12	-

a = isolated yield

In order to expand the scope of this methodology, the Cu-HAP catalyzed C-N coupling protocol was extended to various aryl bromides (Scheme 1). For this we have taken a variety of substituted aryl bromides possessing a wide range of functional groups for our study to demonstrate the scope and the generality of the Cu-HAP catalyzed C-N coupling of aryl bromides with 5,5-dimethylhydantoin in DMF medium, and the results are summarized in **Scheme 1**.

Scheme 1 Substrate scope of aryl bromides

In order to make our catalytic system greener and economical, we focused on reusability of catalyst in C-N coupling of 4-iodo-1-nitro-2-(trifluoromethyl)benzene (**1a**) with 5,5-dimethylhydantoin (**2**). Cu-HAP was recovered quantitatively by simple filtration and reused. The catalyst was found to display significant activity even after the fourth cycle (Table 2, entry 1-4) in DMF medium with no further purification and activation.

Table 2 Recycle of catalyst

S. No.	Cu-HAP	Yield
1	1st time	88
2	2nd time	81
3	3rd time	74
4	4th time	68

Aryl bromides with electron-withdrawing and electron donating groups afforded excellent to good yields of the corresponding N-alkylated diimidones. The position of substituents on the arylbromides play major role in the activity. Furthermore aryl bromides bearing electron-withdrawing groups such as nitro, nitrile, trifluoro methyl in the *para* and *meta* positions gave excellent yields with decreased reaction time compared to the corresponding electron donating groups.

By successful attempt for the synthesis of Nilutamide and various 5,5-dimethyl-substituted phenyl imidazolidine-2,4-diones using heterogeneous catalyst Cu-HAP, we next turned our attention to the preparation of 4-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile (RU56279) [9] in new synthetic approach where Nilutamide was taken as starting material. RU56279 the precursor of 4-[4,4-dimethyl-2,5-dioxo-3-(4-hydroxybutyl)-1-imidazolidinyl]-2-trifluoro methyl benzonitrile (RU58841) [10] and 3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxo-1- imidazolidineacetonitrile (RU58642) [11], is a topically-active non-steroidal antiandrogen with therapeutic applications in the treatment of skin disorders such as acute acne, androgenetic alopecia (male-pattern baldness) and hirsutism (female excess hair).

Scheme 2 Synthesis of RU56279 from Nilutamide (3a)

Nilutamide on reduction with sodium dithionate ($Na_2S_2O_4$) in methanol water gave the compound **4**, which on diazotization using $NaNO_2$/Con. HCl followed by the nucleophilic displacement of diazonium salt by using copper cyanide, afforded the desired compound RU56279 with 72% of yield.

III. Experimental

Materials and methods

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FT IR spectrometer. ^{1}H-NMR spectra on a Bruker 400 MHz, Varian-NMR-inova 500 MHz instruments with TMS as an internal standard and chemical shifts expressed in δ ppm. Mass spectra were recorded on Hewelett Packard mass spectrometer operating at 70 eV.

*General procedure for the synthesis of 5,5-dimethyl-3-arylimidazolidine-2,4-diones (**3a-h**)*

To the solution of aryl bromides **1a-h** (1 mmol) in DMF was added 5, 5-dimethylhydantoin (**2**) (1 mmol) and Cu-HAP (20 mol%). Then the reaction mixture was heated to 100 ^{o}C for 8-16 h. After completion of the reaction as judged by TLC, the reaction mixture was cooled to rt and the catalyst was filtered. The filtrate was diluted with 30 mL of cold water and extracted twice the times with EtOAc (2x20 mL). The combined organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product **3a-h** as off white solids with 68-92% of yields.

5, 5-dimethyl-3-[4-nitro-3-trifluoromethyl) phenyl] imidazolidine-2, 4-done (3a)

Light yellow solid; IR (KBr, cm^{-1}): 3120 (N-H), 1706 (C=O), 1630 (C=O), 1325 (NO_2), 1154 (C-F); ^{1}H NMR (400 MHz, DMSO-d_6); δ 8.81 (s, 1 H), 8.34 (d, *J* = 8.78 Hz, 1 H), 8.22 (s, 1 H), 8.09 (d, *J* = 7.58 Hz, 1 H), 1.48 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 153.7, 146.0, 135.8, 128.9, 125.9, 124.3, 120.1, 58.8, 25.2; ESI-MS: *m/z* 318 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{10}F_3N_3O_4$: C, 45.43; H, 3.18; N, 13.25. Found: C, 45.41; H, 3.16; N, 13.24 %.

5,5-dimethyl-3-phenylimidazolidine-2,4-dione (3b)

Off white solid; IR (KBr, cm^{-1}): 3110 (N-H), 1690 (C=O), 1640 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.84 (d, *J* = 8.78 Hz, 2 H), 7.52-7.66 (m, 3 H), 6.74 (s, 1 H), 1.51 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 155.6, 136.9, 132.9, 127.2, 125.2, 59.2, 25.6; ESI-MS: *m/z* 205 $[M+H]^+$; Anal. Calcd. For $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.66; H, 5.96; N, 13.70 %.

3-(3-methoxyphenyl)-5,5-dimethylimidazolidine-2,4-dione (3c*)*

Off white solid; IR (KBr, cm^{-1}): 3130 (N-H), 1685 (C=O), 1645 (C=O); ^{1}H` NMR (500 MHz, DMSO-d_6); δ 8.76 (s, 1 H), 7.39 (s, 1 H), 6.97 (m, 3 H), 3.79 (s, 3 H), 1.49 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 176.2, 160.0, 129.7, 118.5, 114.2, 112.0, 58.6, 55.4, 25.1, 24.8; ESI-MS: *m/z* 235 $[M+H]^+$; Anal. Calcd. For $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.50; H, 6.06; N, 11.92 %.

4-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)benzonitrile (3d)

Off white solid; IR (KBr, cm^{-1}): 3180 (N-H), 1699 (C=O), 1632 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.77 (d, *J* = 8.78 Hz, 2 H), 7.69 (d, *J* = 7.58 Hz, 2 H), 6.77 (s, 1 H), 1.56 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 175.6, 154.5, 135.9, 132.8, 126.0, 118.2, 111.2, 58.7, 25.1; ESI-MS: *m/z* 230 $[M+H]^+$. Anal. Calcd. For $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.81; H, 4.89; N, 18.30%.

3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)benzoic acid (3e)

Off white solid; IR (KBr, cm^{-1}): 3180 (N-H), 1640 (C=O), 1620 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 11.24 (s, 1 H), 8.64 (s, 1 H), 8.13 (d, *J* = 8.78 Hz, 1 H), 7.64-7.73 (m, 2 H), 6.92 (s, 1 H), 1.59 (s, 6 H); ^{13}C NMR (100

MHz, $CDCl_3$); δ 176.2, 162.3, 153.9, 138.1, 133.6, 131.6, 128.9, 126.8, 116.2, 58.8, 25.0; ESI-MS: *m/z* 249 $[M+H]^+$; Anal. Calcd. For $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.09; H, 4.86; N, 11.26%.

5,5-dimethyl-3-(p-tolyl)imidazolidine-2,4-dione (3f)

Off white solid; IR (KBr, cm^{-1}): 31140 (N-H), 1685 (C=O), 1620 (C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 8.12 (d, *J* = 8.78 Hz, 2 H), 7.92 (d, *J* = 7.58 Hz, 2 H), 6.66 (s, 1 H), 2.34 (s, 3 H), 1.63 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 155.2, 136.1, 133.8, 128.3, 127.1, 58.3, 25.6, 23.2; ESI-MS: *m/z* 219 $[M+H]^+$; Anal. Calcd. For $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: : C, 66.06; H, 6.42; N, 12.81 %.

5,5-dimethyl-3-(4-nitrophenyl)imidazolidine-2,4-dione (3g)

Off white solid; IR (KBr, cm-1): 3109 (N-H), 1716 (C=O), 1624 (C=O), 1345 (NO2); ^1H NMR (400 MHz, $CDCl_3$); δ 8.64 (s, 1 H), 8.01(d, *J* = 8.78 Hz, 2 H), 7.65 (m, 2 H), 6.92 (s, 1 H), 1.51 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 155.0, 139.9, 136.8, 128.3, 125.8, 58.4, 25.3; ESI-MS: *m/z* 250 $[M+H]^+$; Anal. Calcd. For $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 53.00; H, 4.49; N, 16.82 %.

5,5-dimethyl-3-(3-(trifluoromethyl)phenyl)imidazolidine-2,4-dione (3h)

Off white solid; IR (KBr, cm^{-1}): 3160 (N-H), 1670 (C=O), 1631 (C=O); ^1H NMR (500 MHz, DMSO-d_6); δ 8.64 (s, 1 H), 7.84 (s, 1 H), 7.78 (m, 3 H), 1.54 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 175.8, 154.9, 132.2, 129.5, 129.1, 124.7, 122.9, 58.7, 25.1; ESI-MS: *m/z* 273 $[M+H]^+$; Anal. Calcd. For $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.91; H, 4.09; N, 10.26 %.

General procedure for the synthesis of 3-(4-amino-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione (4)

To the solution of Nilutamide **(3a)** in methanol was added $Na_2S_2O_4$ (1 mmol). Then the reaction mixture was stirred for 1h at rt. After completion of the reaction solvent was removed under reduced pressure, and then ice cold water was added. The obtained precipitate was filtered, dried to afford 3-(4-amino-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione (**4**) as off white solid with 94% of yield.

Off white solid; IR (KBr, cm^{-1}): 3120 (N-H), 1680 (C=O), 1644 (C=O); ^1H NMR (500 MHz, DMSO-d_6); δ 8.42 (s, 1 H), 7.37 (s, 1 H), 7.23 (d, *J* = 8.78 Hz, 1 H), 6.93 (d, *J* = 7.58 Hz, 1 H), 5.91 (s, 2 H), 1.40 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 176.3, 155.6, 144.5, 130.9, 125.0, 124.9, 121.2, 117.5, 113.6, 58.7, 25.1; ESI-MS: *m/z* 288 $[M+H]^+$; Anal. Calcd. For $C_{12}H_{12}F_3N_3O_2$: C, 50.18; H, 4.21; N, 14.63. Found: C, 50.12; H, 4.25; N, 14.60 %.

General procedure for the synthesis of 4-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile **(RU56279)**

To the solution of 3-(4-amino-3-(trifluoromethyl)phenyl)-5,5-dimethylimidazolidine-2,4-dione (**4**) in Con. HCl was added aqueous $NaNO_2$ at 0^oC for 5 min. Then the resulting solution was stirred another 15 min, and added aqueous CuCN drop wise at 0^oC. The final solution was stirred for 30 min and diluted with cold water, extracted with EtOAc (2x50 mL). The combined organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product **RU56279** as off white solids with 72% of yield.

Off white solid; IR (KBr, cm^{-1}): 3119 (N-H), 1691 (C=O), 1643 (C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 7.76 (s, 1 H), 7.64 (dd, *J* = 21.5, 7.9 Hz, 2 H), 6.82 (s, 1 H), 1.55 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 175.8, 154.9, 132.3, 132.0, 131.3, 129.6, 129.1, 124.7, 122.9, 58.7, 25.1; ESI-MS: *m/z* 298 $[M+H]^+$; Anal. Calcd. For $C_{13}H_{10}F_3N_3O_2$: C, 52.53; H, 3.39; N, 14.14. Found: C, 52.50; H, 3.44; N, 14.10 %.

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III. Conclusion

In conclusion, we have developed practical and efficient methodology for rapid and green synthesis of Nilutamnide and RU56279 using Cu-HAP as heterogeneous catalyst in DMF medium. The protocol was also applicable for C-N coupling between various aryl bromides and 5, 5-dimethylhydantoin, which affords desired product in moderate to good yields. The catalyst could be reused in the same reaction medium. Further studies aimed at broadening the panel of application of this highly stable, active, inexpensive, heterogeneous and easily prepared copper apatite catalyst are in progress.

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