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One pot synthesis of diaryl ketones from aryl carboxylic acids

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ABSTRACT

Diaryl ketones are synthesized from aryl carboxylic acids in the presence palladium catalyst via Suzuki Cross Coupling under microwave conditions.

Keywords: Aryl carboxylic acid, Pd (dppf)Cl_2,K_2CO_3,Aryl-boronic acid, Suzuki Coupling

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INTRODUCTION

Ketone functionality in organic chemistry has been recognized as a moiety of immense utility. Chemically, it represents a group which gives an immense opportunity to conduct nucleophilic and reductive addition reactions. In order to make the synthetic process less cumbersome and safer we thought of carrying out the reaction in one pot by activating carboxylic acid in situ with 2-chloro-1,3-dimethyl imidazolidinium chloride (DMC), and followed by cross coupling reaction with various boronic acids.

To study the feasibility of this approach, we conducted reaction between phenyl boronic acid and benzoic acid (activated by DMC in situ) with Pd-catalyst in dioxane solvent under microwave.

MATERIALS AND METHODS

General: All reagents were obtained from commercial sources and used without further purification. Melting points were determined using open capillary tubes in paraffin bath and are uncorrected. The monitoring of all reactions was routinely checked by TLC on silica gel-GF 254 (Merck) coated plates. Spotting was visualized using iodine (or) UV lamp. IR spectra were recorded using Perkin- Elmer model-2005 instrument in KBr phase (or) Neat. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 400MHz using $CDCl_3$/ DMSO as solvents. The chemical shift values are reported on δ scale in ppm units, relative to TMS. Reverse phase HPLC analysis was carried out using YMC pack C18 (5µm), 250 x 4.6mm. Column chromatography was performed with silica gel 100-200 mesh size.

General Procedure for the synthesis of (2-Fluoro-3-trifluoromethyl-phenyl)-(4-methoxy-phenyl)-methanone (3a)

A mixture of 2-Fluoro-3-trifluoromethyl-benzoic acid (500mg, 3.37mmol), 1,4-dioxane (30mL), K_2CO_3 (1.39g, 10.11mmol), 2-chloro-1,3-dimethyl imidazolidinium chloride (830 mg, 4.91mmol), 4-methoxyphenylboronic acid (750mg, 6.14mmol) and 1,1-[Bis (diphenylphosphino) ferrocene] dichloropalladium (54mg, 0.06mmol) were stirred at RT for 10 mints. Reaction was purged with nitrogen for 5 mints. Vial was irradiated in microwave at 100^0C for 1h. The reaction mixture was filtered through Celite bed, and washed with ethyl acetate. Filtrate was concentrated under vacuum. The resulting material was purified by flash chromatography ethyl acetate in hexane to give (2-

Fluoro-3-trifluoromethyl-phenyl)-(4-methoxy-phenyl)-methanone (**3a**) off-white solid, (450mg, 65% yield), mp: 153^0C.

Characterization Data for Respective Compounds:

(i) (2-Fluoro-3-trifluoromethyl-phenyl)-(4-methoxy-phenyl)-methanone (**3a**):

The resulting material was purified by flash chromatography ethyl acetate in hexane to give light brown color solid (410 mg, yield-68%), mp: 185^0C.

IR (KBr, cm^{-1}):3330, 3080, 2840, 1673, 1594, 1336, 1140, 877, 753; ^{1}H NMR (400 MHz, DMSO-d_6/ δ/ ppm): 3.91 (s, 3H, OCH_3), 7.46 (m , 3H, ArH), 7.6 (dd, J_1 = 8 Hz, J_2 = 8 Hz, 2H, ArH), 7.65 (dd, J = 12 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6, δ/ ppm): 39.1, 55.6, 114.3, 115.4, 118.0, 122.5, 123.7, 126.1, 126.8, 127.9, 129.3, 136.2, 138.2, 160.1, 163.1, 190.4.

(ii) (4-Chloro-phenyl)-(6-methyl-pyridin-3-yl)-methanone (3b)

The resulting material was purified by flash chromatography ethyl acetate in hexane to give light brown color solid (380 mg, yield-63%), mp: 185^0C.

IR (KBr, cm^{-1}):1675, 1488, 1396, 1297, 1089, 1013, 827; ^{1}H NMR (400 MHz, DMSO-d_6, δ/ ppm): 2.51 (s ,3H, CH_3), 7.15 (d, J = 8.0 Hz, 1H, ArH), 7.35-7.33 (m, J_1 = 8.1 Hz, J_2 = 7.9 Hz, 2H, ArH), 7.42-7.40 (m, J_1 = 7.5 Hz, J_2 = 7.6 Hz, 2H, ArH), 7.60 (d, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H, ArH), 8.44 (d, J = 2.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO d_6, δ/ ppm): 23.5, 122.5, 128.0, 128.4, 130.0, 134.4, 138.6, 145.3, 158.9, 192.5.

(iii) (2-Fluoro-3-trifluoromethyl-phenyl)-(4-methoxy-phenyl)-methanone (3c):

The resulting material was purified by flash chromatography ethyl acetate in hexane to give light brown color solid (389 mg, yield-62%), mp: 189^0C

IR (KBr, cm^{-1}): 3435, 3076, 2972, 1651 ,1598, 1345, 1226, 1125, 848, 753; ^{1}H NMR (400 MHz, DMSO-d_6, δ/ ppm) δ: 3.91 (s, 3H, OCH_3), 7.10 (m, 2H, ArH), 7.56 (t, J= 7.2 Hz, 1H, ArH), 7.65 (dd, J=8.4Hz, 2H, ArH), 7.86 (dd, J = 8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 118.3, 122.8, 123.2, 124.1, 126.4, 129.5, 129.7, 130.4, 133.0, 133.9, 135.3, 160.5, 190.7.

(iv) (3-bromophenyl) (2-fluoro-3-(trifluoromethyl)phenyl) methanone (3d):

The resulting material was purified by flash chromatography ethyl acetate in hexane to give off-white color solid (426 mg, yield-66%), mp: 166^0C

IR (KBr, cm^{-1}): 3076, 1669, 1618, 1463, 1331, 1262, 1129, 750, 672, 636; ^{1}H NMR (400 MHz, DMSO-d_6, δ/ ppm): 7.40 (d, J = 8.4 Hz, 1H, ArH), 7.63- 7.52 (m, J_1 = 7.4 Hz, J_2 = 7.2Hz, 2H, ArH), 7.96-7.99 (m, 3H, ArH), 8.04 (t, J = 7.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 118.5, 122.7, 123.0, 124.3, 126.4, 129.5, 129.0, 130.2, 133.0, 133.7, 135.2, 160.5, 190.6.

(v) Cyclopropyl(1-methyl-1H-pyrazol-5-yl) methanone (3e):

The resulting material was purified by flash chromatography ethyl acetate in hexane to give light brown color solid (389 mg, yield-62%), mp: 186^0C

IR (KBr, cm^{-1}): 3056, 1680, 1615, 1493, 1321, 1232, 1128, 753, 686, 654; ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 1.0 (m, 2H), 1.22 (m, 2H), 2.52 (m, 1H), 4.20 (s, 3H, CH_3), 7.01 (s, 1H, ArH), 7.51 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 12.2, 12.2, 15.4, 40.3, 113.4, 137.7, 153.7, 200.7.

(vi) (6-Chloro-pyridazin-3-yl)-phenyl-methanone (3f):

The resulting material was purified by flash chromatography ethyl acetate in hexane to give light orange color solid (415 mg, yield-68%), mp: 166^0C

IR (KBr, cm^{-1}): 2922, 2592, 1680, 1525, 1439, 1009; ^{1}H NMR (400 MHz, DMSO-d_6/ ppm/ δ): 7.79-7.71 (d, J_1 = 8 Hz, 1H), 7.56-7.54 (d, J_1 = 7.0 Hz, 1H), 7.47-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 128.6, 129.7, 130.5, 132.7, 133.4, 134.8, 148.8, 160.1, 185.7.

(vii) (2-fluorophenyl)(pyridin-4-yl)methanone (3g):
The resulting material was purified by flash chromatography ethyl acetate in hexane to give brown color solid (415 mg, yield-69%), mp: 172^{0}C.

IR (KBr, cm^{-1}): 3425, 3066, 2992, 1651 ,1558, 1335, 1216, 1115, 858, 753; ^{1}H NMR (400 MHz, DMSO-d$_6$/ ppm/ δ): 7.20 (m, 1H, ArH), 7.32 (m, 1H, ArH), 7.62-7.58 (m, 4H, ArH), 8.81 (d, *J* = 1.6 Hz, 1H, ArH), 8.81 (d, *J* = 1.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$, δ/ppm): 115.4, 121.4, 123.3, 123.8, 124.3, 129.1, 134.2, 145.0, 149.8, 149.8, 156.3, 190.3

(viii) tert-butyl 4-(4-bromobenzoyl) piperidine-1-carboxylate (3h):
The resulting material was purified by flash chromatography ethyl acetate in hexane to give off-white color solid (415 mg, yield-69%), mp: 179^{0}C

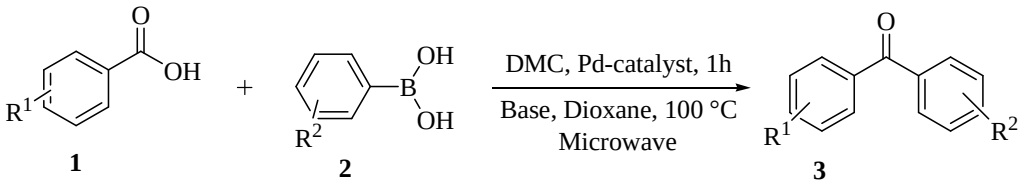
^{1}H NMR (400 MHz, DMSO-d$_6$, δ/ppm): 1.50 (s, 9H, 3CH$_3$), 1.80 (m, 2H, CH$_2$), 1.91 (m, 2H, CH$_2$), 2.92 (m, 2H, CH$_2$), 3.41 (m,1H, CH), 4.22 (s, 2H, CH), 7.51 (m, 1H, ArH), 7.63 (m, 2H, ArH), 7.85 (m 1 H, ArH). ^{13}C NMR (100 MHz, DMSO-d$_6$, δ/ppm): 27.9, 27.9, 28.4, 43.7, 46.0, 46.0, 127.5, 129.8, 129.8, 131.5, 131.5, 135.7, 159.6, 202.1.

(ix) (4-chlorophenyl) (6-methoxypyridin-3-yl) methanone (3i):
The resulting material was purified by flash chromatography ethyl acetate in hexane to give light brown color solid (340 mg, yield-56%), mp: 164^{0}C

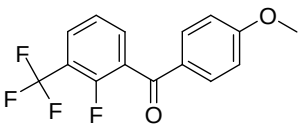
IR (DCM, cm^{-1}): 2945, 2845, 1690, 1573, 1489, 1394, 1287, 1090, 1025, 828; ^{1}H NMR (400 MHz, DMSO-d$_6$, δ/ ppm): 3.82 (s, 3H, CH$_3$), 6.72 (d, *J* = 8.8 Hz, 1H, ArH), 7.34 (d, 2H *J* = 8.8 Hz, ArH), 7.41 (d, *J* = 8.4 Hz, 2H, ArH), 7.62 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, ArH), 8.15 (d, *J* = 2.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d$_6$, δ/ppm): 53.3, 110.9, 127.9, 128.6, 132.8, 133.3, 137.4, 143.4, 144.9, 163.4, 185.2.

RESULTS AND DISCUSSION

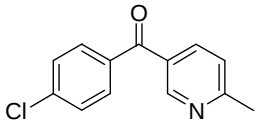
Scheme-1



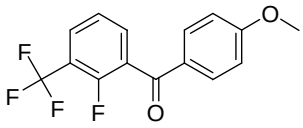
Scheme 1: Preparation of Diaryl Ketones via Suzuki Cross Coupling



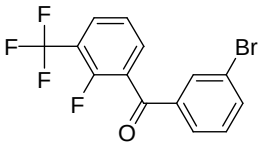
3a



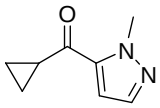
3b



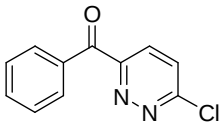
3c



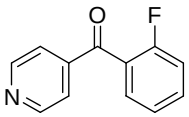
3d



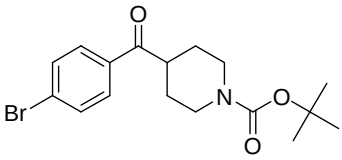
3e



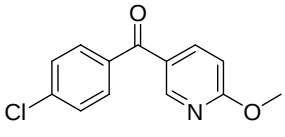
3f



3g

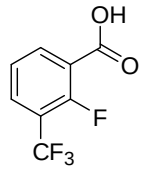


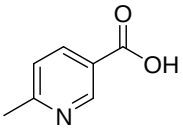
3h

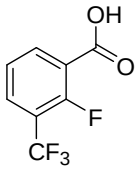


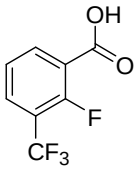
3i

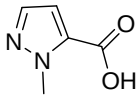
R1=

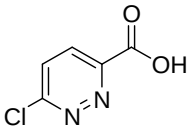


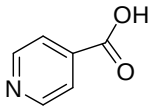


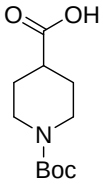


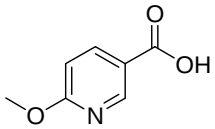




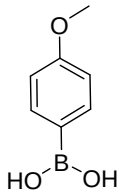


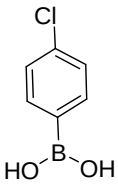


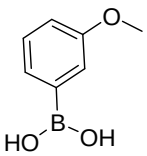


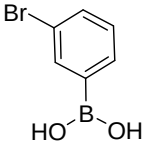


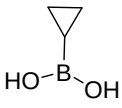
R2=

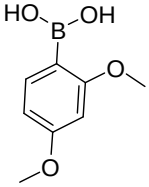


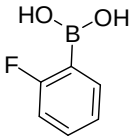


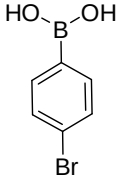


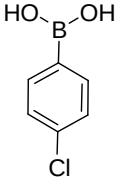












CONCLUSION

In the present study, we conducted reaction between phenyl boronic acid and benzoic acid (activated by DMC in situ) with Pd-catalyst in dioxane solvent under microwave to give diaryl ketenes.

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