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Synthesis of *N*-Methyl-6-heterocyclic-1-oxoisoindoline Derivatives by Microwave Assisted Buchwald-Hartwig Amination

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Abstract: An rapid and efficient microwave assisted Pd(II) catalyzed protocol for the preparation of *N*-methyl-6-heterocyclic-1-oxoisoindoline derivatives by Buchwald-Hartwig amination with an overall yield 68-85% has been described.

Keywords: Synthesis, *N*-methyl-6-heterocyclic-1-oxoisoindoline, 2-(2'-Di-tert-butylphosphine) biphenylpalladium(II) acetate, Buchwald–Hartwig amination

Introduction

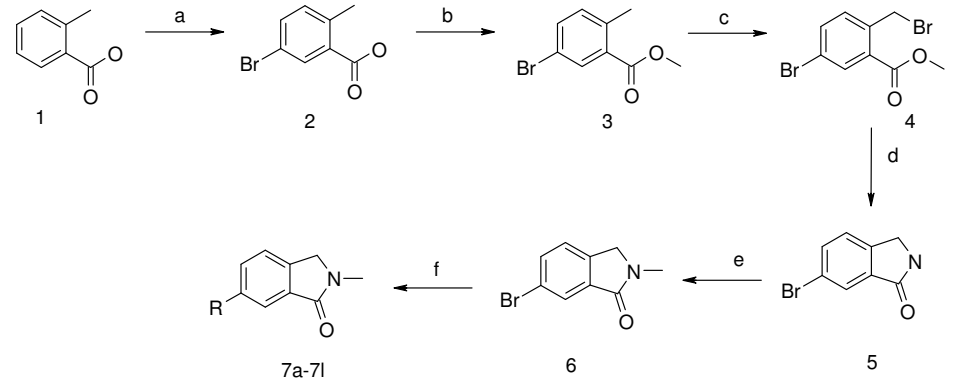
Oxoisoindoline derivatives plays an important role in organic chemistry due to their wide range of biological applications. Isoindolinone like structures are very good antiviral drugs for the treatment of cold[1] important anti-inflammatory agents[2] analgesic agents[3] and recent study reveals that 3-oxoisoindoline-4-carboxamide core structure, displayed a good activity as poly (ADP-ribose) polymerase (PARP) inhibitors[4].

Microwave-assisted amination of aromatic halides has become a powerful methodology for the construction of aryl amine intermediates useful for the synthesis of biologically active molecules[5]. Microwave-assisted organic synthesis has gained considerable attention over the past decade and these advances have also found application in the pursuit of pharmaceutically active agents[6,7]. The power and complexity of reactions adapted to microwave methods has grown over the past few years in particular, expanding the scope of their use from simple acceleration of coupling reactions to include more elegant applications such as the acceleration of momentous metal-catalyzed transformations[8].

Experimental

Melting points were determined on the electrothermal melting point apparatus and were uncorrected. Infrared spectra were recorded on the Shimadzu-470 infrared spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 solvent on varian XL-300 MHz spectrometers/ varian XL-400 MHz (chemical shifts are given in parts per million (ppm)).

Herein, we described microwave assisted Buchwald-Hartwig amination reaction of *N*-methyl-6-heterocyclic-1-oxoisoindoline derivatives through an intermediate, 6-bromoisoindoline-1-one (**5**). Starting material 6-bromoisoidoline-1-one (**5**) was synthesized by known procedure[9]. Synthesis of **5** starts with the bromination of commercially available 2-methylbenzoic acid (**1**) with Br_2/Fe as shown in Scheme 1. Esterification of 5-bromo-2-methylbenzoic acid (**2**) with $SOCl_2$/MeOH followed by bromination reaction at the benzylic position with NBS under radical condition (AIBN)[10] was carried out to obtain methyl-5-bromo-2-(bromoethyl)benzoate (**4**). This intermediate was treated with aq NH_4OH in THF/MeOH afforded the required intermediate 6-bromoisoindoline-1-one (**5**) in 94% isolated yield. To further explore, the intermediate **5** was converted to *N*-methyl-6-bromoisoindoline-1-one **(6)** and Buchwald-Hartwig amination reaction of which with a number of cyclic amines by microwave irradiation method produces *N*-methyl-6-heterocyclic-1-oxoisoindoline derivatives **(7a-l)** in good isolated yield, as described in Scheme 1.



Scheme 1. Reagents and conditions (a) Br_2/Fe, RT, 12 h; (b) $SOCl_2$/MeOH, 65 °C, 3 h; (c) NBS/CCl_4/AIBN, 75 °C, 4 h; (d) MeOH/THF/NH_4OH, 50 °C, 4 h; (e) NaH/DMF/MeI, 0 °C, 1 h; (f) NaO-*t*-Bu/2-(2'-di-tert-butylphosphine)biphenylpalladium(II) acetate /toluene: *t*-BuOH (5:1)/R (Amine), microwave radiation, 140 °C, 15 min.

*General procedures for the synthesis of the N-methyl 6-heterocyclic-1-oxoisoindoline (**7a-l**)*

A high pressure microwave 5 mL process vial was loaded with 6 (1 equiv) and amine (1.2 equiv in anhydrous toluene/*t*-BuOH (5:1). 2-(2'-Di-tert-butylphosphine) biphenyl-palladium(II) acetate (5 mol%) and NaO-*t*-Bu (1.5 equiv) were added and then the process vial was evacuated, backfilled with argon and sealed. The mixture was kept at 140 ^oC for 15 min (including the ramp time). After cooling, the mixture was diluted with ethyl acetate, filtered through celite and the solvent was removed under reduced pressure. The product was isolated by flash chromatography on silica gel with hexane/ethyl acetate solvent mixtures.

Analytical data

6-(4-(Dibenzylamino) piperidin-1-yl)-2-methylisoindolin-1-one(***7a***)

White solid, mp. 133.4-134.8 °C; IR (KBr) ν_{max} (cm^{-1}): 1618, 1664, 2834, 2924, 3012; ^1H NMR (400 MHz, DMSO-d_6): δ 1.67-1.86 (m, 4H), 2.49-2.60 (m, 3H), 3.03 (s, 3H), 3.61 (s, 4H), 3.79 (d, J = 12.32 Hz, 2H), 4.30 (s, 2H), 7.07 (d, J = 2.20 Hz, 1H), 7.15-7.21 (m, 3H),

7.28-7.37 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.9, 29.0, 49.0, 50.8, 53.2, 56.3, 108.5, 119.7, 123.4, 126.6, 128.07, 128.09, 131.5, 133.3, 140.5, 151.0, 167.6; LC-MS *m/z*: found 426.2, 427.2 $[M+H]^+$, calcd for $C_{28}H_{31}N_3O$ 425.2.

2-Methyl-6-morpholinoisoindolin-1-one(***7b***)

Off white Solid, mp. 126.8-128.3 °C; IR (KBr) ν_{max} (cm^{-1}): 1625, 1679, 2854, 2972 and 3066; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.05 (s, 3H), 3.14 (t, J = 4.76 Hz, 4H), 3.74 (t, J = 4.88 Hz, 4H), 4.33 (s, 2H), 7.11 (s, 1H), 7.20 (d, J = 2.40, 1H), 7.41 (d, J = 8.36 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.0, 48.7, 50.8, 66.0, 108.0, 118.9, 123.5, 132.2, 133.3, 151.2, 167.6; LC-MS *m/z*: found 233.2 $[M+H]^+$, calcd for $C_{13}H_{16}N_2O_2$ 232.27.

6-(2,6-Dimethylmorpholino)-2-methylisoindolin-1-one(***7c***)

Off white Solid, mp. 148.5-150.2 °C; IR (KBr) ν_{max} (cm^{-1}): 1623, 1679, 2927, 2974 and 3060; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (d, 6H), 3.05 (s, 3H), 3.10-3.36 (m, 2H), 3.65 (d, J = 11.76 Hz, 4H), 2.34 (s, 2H), 7.13 (d, J = Hz, 1H), 7.21 (d, J = 8.00 Hz, 1H), 7.40 (d, J = 7.56 Hz, 1H);^{13}C NMR (100 MHz, DMSO-d_6): δ 19.3, 29.5, 51.3, 54.4, 71.4, 108.5, 119.4, 124.0, 132.4, 133.9, 151.3, 168.1; LC-MS *m/z*: found 261.2 $[M+H]^+$, calcd for $C_{15}H_{20}N_2O_2$ 260.33.

6-(Benzyl (ethyl)amino)-2-methylisoindolin-1-one(***7d***)

Pale yellow viscous liquid**,** IR (neat) ν_{max} (cm^{-1}): 1624, 1674, 2854 and 2921; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, J = 15.00 Hz, 3H), 3.03 (s, 3H), 3.53 (q, J = 7.00 Hz, 2H), 4.27 (s, 2H), 4.59 (s, 2H), 6.81 (s, 1H), 6.89 (d, J = 2.44 Hz, 1H), 7.20-7.33 (m, 6H);^{13}C NMR (100 MHz, DMSO-d_6): δ 11.9, 27.0, 28.4, 29.0, 45.3, 50.7, 53.3, 104.7, 115.4, 123.5, 126.3, 126.6, 128.4, 138.9, 147.9, 167.8; LC-MS *m/z*: found 281.2 $[M+H]^+$, calcd for $C_{18}H_{20}N_2O$ 280.36.

6-(Ethyl(2-hydroxyethyl)amino)-2-methylisoindolin-1-one(***7e***)

Off white solid, mp. 123.3-124.8 °C; IR (KBr) ν_{max} (cm^{-1}): 1499, 1660,2863 and 3311; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.94 (s, 3H), 3.03 (s, 3H), 3.41 (t, J = 8.76 Hz, 2H), 3.52 (t, J = 7.56 Hz, 2H), 4.28 (s, 2H), 4.68 (t, J = 7.20 Hz, 1H), 6.86 (s, 1H), 6.93 (d, J = 3.12 Hz, 1H), 7.31 (d, J =11.12 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.9, 26.1, 27.1, 29.0, 46.3, 50.7, 107.4, 118.4, 124.3, 130.3, 132.1, 150.1,168.1.; LC-MS *m/z*: found 221.2 $[M+H]^+$, calcd for $C_{12}H_{16}N_2O_2$ 220.26.

6-(4-Methoxypiperidin-1-yl)-2-methylisoindolin-1-one(***7f***)

White solid, mp. 133-135 °C; IR (KBr) ν_{max} (cm^{-1}): 1667, 2803 and 2937; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.51 (q, J = 5.08 Hz, 2H), 1.91 (q, 2H), 2.91 (t, 2H), 3.03 (s, 3H), 3.25 (s, 3H), 3.31-3.33 (m, 1H), 3.50 (t, J = 8.20 Hz, 2H), 4.30 (s, 2H), 7.09 (s, 1H), 7.18 (d, J = 11.12 Hz, 1H), 7.36 (d, J = 11.12 Hz, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.9, 29.9, 46.5, 50.8, 54.8, 75.3, 108.4, 119.6, 123.5, 131.5, 133.3, 151.0,167.6; LC-MS *m/z*: found 261.2 $[M+H]^+$, calcd for $C_{15}H_{20}N_2O_2$ 260.33.

6-(Isobutyl (methyl)amino)-2-methylisoindolin-1-one(***7g***)

Pale yellow viscous liquid, IR (neat) ν_{max} (cm^{-1}): 1580, 1627,1679, 2868 and 2954; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (d, J = 6.64 Hz, 6H), 1.97-2.04 (m, 1H), 2.95 (s, 3H), 3.05 (s, 3H), 3.17 (d, J = 7.36 Hz, 2H), 4.29 (s, 2H), 6.83 (s, 1H), 6.91 (d, J = 8.44 Hz, 1H), 7.32 (d, J = 8.40 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.0, 26.6, 28.4, 29.0, 50.7, 59.7, 104.2, 115.2, 123.4, 128.1, 133.34, 149.2, 167.9; LC-MS *m/z*: found 233.2 $[M+H]^+$, calcd for $C_{14}H_{20}N_2O$ 232.32.

2-Methyl-6-(1,4-oxazepan-4-yl)isoindolin-1-one(***7h***)

Pale yellow viscous liquid, IR (neat) ν_{max} (cm^{-1}): 1661, 2826, 2939, 3068 and 3468; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.05 (p, J = 5.96 Hz, 2H), 3.19 (s, 3H), 3.65-3.69 (m, 6H), 3.83-3.86 (m, 2H), 4.28 (s, 2H), 6.88 (d, J = 8.40 Hz, 1H), 7.14 (d, J = 2.52 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.0, 23.1, 26.4, 28.1, 49.2, 54.7, 58.7, 104.6, 114.2, 125.5, 127.1, 131.34, 147.6, 167.7; LC-MS *m/z*: found 247.2 $[M+H]^+$, calcd for $C_{14}H_{18}N_2O_2$ 246.30.

2-Methyl-6-(pyrrolidin-1-yl)isoindolin-1-one(***7i***)

Off white solid, mp. 115.7-117.2 °C; IR (KBr) ν_{max} (cm^{-1}):1628, 1677, 2848, 2946 and 3069; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.96 (p, J = 4.60 Hz, 4H), 3.03 (s, 3H), 3.24 (t, J = 8.60 Hz, 4H), 4.29 (s, 2H), 6.69 (s, 1H), 6.74 (d, J = 11.04 Hz, 1H), 7.32 (d, J = 11.00 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.69, 29.26, 51.18, 53.82, 103.16, 115.37, 124.68, 131.07, 134.24, 151.51, 168.39; LC-MS *m/z*: found 217.2 $[M+H]^+$, calcd for $C_{13}H_{16}N_2O$ 216.27.

2-Methyl-6-thiomorpholinoisoindolin-1-one(***7j***)

Off white semi solid, IR (neat) ν_{max} (cm^{-1}):1623, 1666, 2854, 2923 and 3059; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (t, 4H), 3.19 (s, 3H), 3.62 (t, J = 5.22 Hz, 4H), 4.30 (s, 2H), 7.10 (s, 1H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 47.3, 51.2, 66.3, 108.0, 118.9, 123.5, 132.2, 133.3, 151.2, 167.6; LC-MS *m/z*: found 249.2 $[M+H]^+$, calcd for $C_{13}H_{16}N_2OS$ 248.34.

6-(1,1-Dioxidothiomorpholin-4-yl)-2-methyl-2,3-dihydro-1H-isoindol-1-one(***7k***)

Off white solid, mp. 203.7-205.3 °C; IR (KBr) ν_{max} (cm^{-1}):1625, 1692, 2839, 2928, 2995, 3053 and 3565; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.04 (s, 3H), 3.12 (t, J = 4.65 Hz, 4H), 3.81 (t, J = 5.16 Hz, 3H), 4.33 (s, 2H), 7.22 (s, 1H), 7.26 (d, J = 8.31 Hz, 1H), 7.43 (d, J = 8.25 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.0, 49.2, 51.8, 66.4, 107.5, 119.4, 124.2, 131.8, 134.1, 150.2, 167.9; LC-MS *m/z*: found 281.2 $[M+H]^+$, calcd for $C_{13}H_{16}N_2SO_3$ 280.34.

6-(Azetidin-1-yl)-2-methylisoindolin-1-one(***7l***)

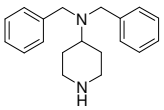
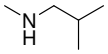
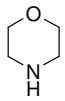
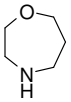
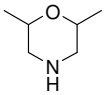
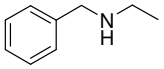
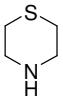
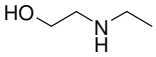
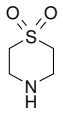
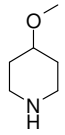
White solid, mp. 139.8-141.6 °C; IR (KBr) ν_{max} (cm^{-1}): 1620, 1676, 2845, 2918, 3039 and 3389; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27-2.32 (m, 2H), 3.03 (s, 3H), 3.79-3.84 (m, 4H), 4.29 (s, 2H), 6.59 (d, J = 2.73 Hz, 1H), 6.61 (s, 1H), 7.32 (d, J = 8.67 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 16.89, 29.46, 51.38, 52.62, 104.46, 115.07, 123.78, 130.27, 133.64, 152.51, 168.19; LC-MS *m/z*: found 203.2 $[M+H]^+$, calcd for $C_{12}H_{14}N_2O$ 202.25.

Results and Discussion

Initially to conduct Buchwald-Hartwig amination reaction, various reaction conditions were attempted for the synthesis of 2-methyl-6-morpholin-4yl-isoindolin-1-one (**7b)** from *N*-methyl-6-bromoisoindoline-1-one (**6**). Furthermore, we explored the influence of different base, ligand and Pd catalyst. Here, both thermal and microwave assisted reactions were carried out in sealed tube by taking *N*-methyl-6-bromoisoindoline-1-one (1 equiv), cyclic amine morpholine (1.2 equiv) under various reaction conditions *i.e.,* K_2CO_3, DMF, 140 ^oC; $Pd_2(dba)_3$, (S)-(R)-PPFA, NaO-*t*-Bu/KO-*t*-Bu, toluene; $Pd_2(dba)_3$, BINAP, NaO-*t*-Bu/KO-*t*-Bu, toluene; $Pd_2(dba)_3$, XantPhos, NaO-*t*-Bu/KO-*t*-Bu, toluene; Pd(OAc), BINAP, NaO-*t*-Bu/KO-*t*-Bu, toluene; $Pd(OAc)_2$, CyJohnPhos, NaO-*t*-Bu/KO-*t*-Bu, toluene; $Pd(OAc)_2$,

XantPhos, NaO-*t*-Bu/KO-*t*-Bu, toluene; 2-(2'-di-tert-butylphosphine)biphenylpalladium(II) acetate, NaO-*t*-Bu, toluene, 140 °C, 16 h (thermal reaction); 2-(2'-di-tert-butylphosphine) biphenylpalladium(II) acetate, NaO-*t*-Bu, toluene/*t*-BuOH (5:1), microwave 140 °C, 15 min. Unfortunately, none of the above reaction conditions both in thermal and microwave irradiation methods gave product except later two reaction conditions and we are unable to predict the reason for not obtaining any product. Thermal reaction for the preparation of **7b** under the conditions, 2-(2'-di-tert-butylphosphine)biphenylpalladium(II) Acetate (5 mol%), NaO-*t*-Bu (1.5 equiv), toluene, 140 °C, 16 h afforded only 18% isolated yield but the same conditions in microwave assisted reaction resulted in significant increase in the product yield (68-85% isolated yield). In many cases the use of microwave heating in palladium-catalyzed reactions, including buchwald-hartwig aminations provides improvements in the yields and reaction times[11]. Since toluene is poor microwave absorption stability, we tried toluene/*t*-BuOH (5:1) solvent mixture for the synthesis and it provided the products (**7a-l)** in high yields. Results are shown in Table 1.

Table 1. Synthesis of *N*-methyl 6-heterocyclic-1-oxoisoindoline

Entry	R	Product[a]	Yield[b] %	Entry	R	Product[b]	Yield %
1		**7a**	78	7		**7g**	68
2		**7b**	85	8		**7h**	72
3		**7c**	82	9		**7i**	81
4		**7d**	76	10		**7j**	68
5		**7e**	75	11		**7k**	67
6		**7f**	78	12		**7l**	85

***6** (1 Equiv), amine (1.2 equiv), NaO-t-Bu (1.5 equiv), 2-(2'-di-tert-butylphosphine) biphenyl-lpalladium(II) Acetate (5 mol%), Toluene/t-BuOH (5:1), Microwave radiation, 140 °C, 15 min*
[a]Products were confirmed by spectral characterization (^{1}H & ^{13}C NMR, LCMS and IR)
[b] Chromatographically isolated yield of pure product.

Conclusion

In conclusion, the use of microwave irradiation allowed a rapid and high-yield preparation of *N*-methyl-6-heterocyclic-1-oxoisoindoline derivatives. We carried out the Buchwald amination

with alkyl and aryl amines using Pd(II) catalyst by conventional protocol as well as by microwave irradiation. Dramatic improvements on excellent yields using microwave irradiation were observed. Different reaction conditions, quantities of substrates and solvents were tested to develop a simple and reproducible Buchwald amination methodology. Our interest was to optimize the construction of alkyl or aryl amine intermediates which may useful for the synthesis of biologically active molecules and the studies is under progress.

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