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Intramolecular Heck Reaction of Arylbromides as a Route to Isoquinolinone Derivatives

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ABSTRACT A very short and efficient methodology based on intramolecular palladium catalyzed cyclization of arylbromides has been developed for the preparation of various pharmaceutically important isoquinolinone derivatives using Jeffrey's protocol.

KEYWORDS Intramolecular heck reaction, Isoquinolinones, Jeffrey's condition, Wacker oxidation.

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INTRODUCTION

Heck reaction is a powerful weapon in the arsenal of organic chemists for the formation of C-C bonds.[1-9] Among the aryl halides, aryl iodides have so far been mostly employed for the Heck coupling, because it has the least C-X bond strength in the halide series.[10] On the other hand, Heck chemistry of arylbromides or chlorides is relatively less explored, although they are much cheaper and more readily available. Arylbromides and chlorides are less reactive and they undergo oxidative addition step more reluctantly due to higher C-X bond strength. Hence, high activation is necessary, but at high temperature, P-C bond cleavage occurs in the ligated PPh_3. As a result, aryl scrambling occurs and different bi-products are formed.[11-14] Therefore, Heck reaction for arylbromides is less abundant. Isoquinolinones are important target molecules for the synthetic community due to wide range of biological activities they exhibit.[15-20] Many methods are available for their synthesis.[21-27] Majumdar's group reported Pd-catalyzed cyclization of aryliodide[28] to isoquinolinone derivatives. Pd-catalyzed intramolecular cyclizations of vinyl bromides for the synthesis of heterocycles have also been reported.[29,30] Herein, we report the use of less reactive appropriate arylbromides for the access of different *N*-arylisoquinolinone derivatives, some of which are new.

RESULTS AND DISCUSSION

We first focused on the preparation of Heck precursors by *N*-allylation of *N*-aryl-2-bromobenzamides. Thus, 2-bromobenzoic acid was first converted into the acid chloride**2**; the latter was then used for *N*-benzoylation of different *para*-substituted anilines. The compounds **4a-e w**as then treated with allyl bromide in the presence of sodium hydride to give smoothly the corresponding *N*-allyl-*N*-aryl-2-bromobenzamides (**5a-e)** [**Scheme 1**]. Compounds **5a-e** is arylbromides in terms of Heck reaction with an allylic residue at the appropriate position. We, then, attempted intramolecular Pd-catalyzed cyclization[30-33] on **5a (**R = Cl**)** in different conditions [**Table 1**]. The reaction best proceeded by refluxing **5a** in presence of $Pd(OAc)_2$ (Entry 7, yield 88%) in DMF using KOAc as base and n-Bu_4NBr as additive (Jeffrey's condition)[34]

Reagents and conditions: (i) *o*-bromobenzoic acid (**1)** (2.01 g, 10 mmol), $SOCl_2$ (20 mL, as solvent and reagent), reflux, 1 h; (ii) 2-bromobenzoyl chloride (**2)** (1.1 g, 5 mmol), anilines (1.5 eq), Et_3N (2eq, 10 mmol, 1.4 mL); and (iii) 2–bromo-*N*-arylbenzamide (**4)** (2 mmol), NaH (95% dispersion in oil, 1.5 eq, 3 mmol, 75.8 mg), allyl bromide (1.5 eq, 3 mmol, 260 µL), dry DMF (5 ml), 0°C to rt, 3 h.

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m), 7.04 (1H, s), 2.31 (3H,s).^{13}CNMR (150 Hz, $CDCl_3$): δ 161.7, 140.4, 137.4, 132.6, 132.4, 129.3, 128.7, 128.6, 127.2, 126.3, 123.2, 121.7, 112.5, 15.4.

6e: White solid; Yield: 78 mg (72%); mp 127°C.IR (KBr): 1661, 1632, 1603, 1253 cm^{-1}.^{1}H NMR (400MHz, $CDCl_3$): δ 8.52 (1H, d, *J* = 8.0 Hz), 7.74 (1H, t, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 8.0 Hz), 7.74 (1H, t, *J* = 7.6 Hz) 7.43 (2H, d *J* = 8.8 Hz), 7.01–6.97 (3H, m), 3.86 (3H,s), 2.31 (3H, s).^{13}CNMR (100 MHz, $CDCl_3$): δ 162.1, 159.0, 137.5, 134.4, 132.4, 130.3, 128.7, 127.9, 126.9, 126.4, 123.1, 114.4, 111.9, 55.6, 15.4.

7:Viscous liquid; Yield: 84 mg (62%). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.53 (1H, d, *J* = 8.0 Hz), 7.79–7.72 (2H, m), 7.581 (1H, dt, *J* = 7.4, 1.2 Hz), 7.54–7.50 (2H, m), 7.45–7.43 (2H, m),7.36 (1H, s), 5.23 (2H, s), 2.10 (3H, s).

Procedure for the Heck reaction of *N*-allyl-2-bromo-*N*-phenylbenzamide (5d)

A stirred solution of *N*-allyl-2-bromo-*N*-phenylbenzamide **5d** (158 mg, 0.5 mmol) in DMF (4 mL) was added KOAc (49.07 mg, 0.5 mmol, 1eqv), PPh_3(32.8 mg, 0.125 mmol, 0.25 eqv), and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol%) at room temperature. Then, the mixture was heated to 120°C for 12 h. After the completion of the reaction, the mixture was cooled and water (20 mL) was added, extracted with EtOAc (3 × 20 mL). The extracts were dried with Na_2SO_4) and concentrated under reduced pressure to give a residue that was purified by column chromatography over silica gel (100–200 mesh) using PE–EtOAc (6:1) as eluent to afford the 4 –methyl-2-phenylisoquinolin-1(2*H*)-one (**6d**). Yield: 96 mg (82%)

CONCLUSION

We have synthesized some quinolinone derivatives using intramolecular Heck reaction of appropriately substituted aryl bromides employing Jeffery's protocol. Although usually the reaction proceeded without any ligand, in case of simple, *N*-phenyl system Jeffery's condition did not work. To obtain an appreciable yield of the corresponding isoquinoline derivative, introduction of ligand like triphenylphospine is necessary. Further manipulation of the prepared compounds may be useful for the construction of the more variety of heterocyclic compounds and also may be useful for biological studies. Further studies on the application of synthesized compounds are underway in this laboratory.

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