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Pd-Catalyzed Carbonyl Insertion Coupling Reactions of a Hypervalent Iodoheterocycle with Alcohols and Amines

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Abstract:. The palladium-catalyzed cross-coupling carbonyl insertion reaction between 3,7-bis(*N,N*-dimethylamino)-10*H*-dibenz[b,e]iodinium iodide (**1**) and alcohols or amines **2** is described. Some new amides and esters **3** containing an active iodo functional group have been prepared in 65-91% yields.

Keywords: Cross-coupling; hypervalent iodoheterocycle; carbonyl insertion; amides; esters

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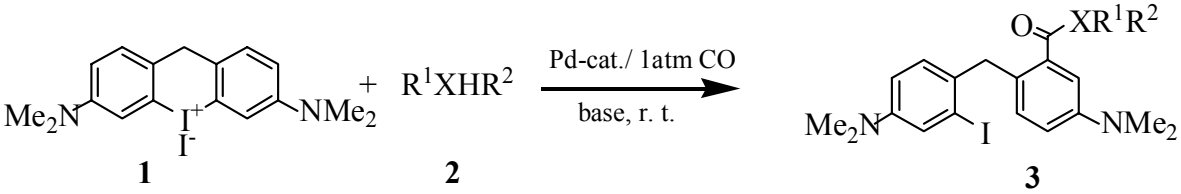
Introduction

In the past few decades, much attention has been focused on palladium-catalyzed carbonylation reactions [1,2], which provide a simple method for synthesizing some complicated compounds [3-6]. These kinds of reactions have been carried out only when the substrates are aryl halides, heteroaryl halides, alkene halides, arylfluoromethylsulfonates and hypervalent iodinium salts, etc. [7], However, the reactions of cross-coupling and carbonyl insertion in one step for iodoheterocyclic compounds has not been reported so far. In the present work, we will describe such a palladium-catalyzed cross–coupling carbonylative insertion reaction between an iodoheterocyclic compound and alcohols or amines.

Results and Discussion

The cross-coupling carbonyl insertion reactions of 3,7-bis(*N,N*-dimethylamino)-10*H*-dibenz[b,e] iodinium iodide (**1**) and alcohols or amines **2** proceed as shown in Scheme 1. The new compounds obtained by carbonyl insertion still have an active iodo functional group, which can serve for the intermediate to undergo further reactions.

Scheme 1



1 **2** **3**

X=O, R^2=0, R^1= Me (**3a**), Et (**3b**), *i*-Pr (**3c**), *n*-Pr (**3d**), Et_2N CH_2CH_2 (**3e**); X = N, R^1 = H, R^2= *n*-Pr (**3f**), *n*-Bu (**3g**), Ph (**3h**), *p*-Tolyl (**3i**), *m*-Tolyl (**3j**), *m*-EtOPh (**3k**), *o*-ClPh (**3l**), benzothiazol-2-yl (**3m**); X = N, R^1 = Me, R^2= Ph (**3n**), R^1=R^2= Et (**3o**)

These carbonylation reactions were carried out smoothly at mild temperature and gave satisfactory yields (65-91%). We examined the influences of catalyst, base and reaction time on this reaction through the cross-coupling of **1** with alcohols. The results obtained under different conditions are summarized in Table 1. Several different Pd-catalysts were used and all of them catalyzed this reaction, but slightly different influences on the yield were observed. $Pd(OAc)_2$ was the best choice for the reaction. As for the type of base, when the alcohol was **2a**, **2b**, **2d** or **2e**, then Bu_3N, Et_3N or Na_2CO_3 could be used. When the alcohol was **2c**, only *i*-PrONa could be used. It was noted that primary alcohols showed much higher reactivity than secondary or tertiary alcohols in this carbonylation.

Table 1. Reactions of compound **1** with various alcohols

ROH	Catalyst (2 mmol)	Base (2 equiv)	React. time (hr)	Product	Yield (%)
2a	$Pd(OAc)_2$	Bu_3N	2.0	**3a**	81
2a	$Pd(OAc)_2$	Et_3N	2.0	**3a**	78
2a	$Pd(OAc)_2$	Na_2CO_3	2.0	**3a**	68
2a	$PdCl_2$	Bu_3N	2.0	**3a**	52
2a	$Pd(PPh_3)_4$	Bu_3N	2.0	**3a**	62
2a	$Pd(PPh_3)_2Cl_2$	Bu_3N	2.0	**3a**	60
2b	$Pd(OAc)_2$	Bu_3N	3.0	**3b**	78
2c	$Pd(OAc)_2$	*i*-PrONa*	1.0	**3c**	60
2d	$Pd(OAc)_2$	Bu_3N	3.5	**3d**	70
2e	$Pd(OAc)_2$	Bu_3N	3.5	**3e**	65

* Amount of *i*-PrONa was 0.5 equiv.

Conclusions

An interesting and effective methodology for the synthesis of some new amides and esters, **3**, containing an active iodo functional group via the palladium-catalyzed cross-coupling carbonyl insertion reactions between 3,7-bis(*N,N*-dimethylamino)-10*H*-dibenz[b,e] iodinium iodide (**1**) and alcohols or amines **2** is described. This reaction is simple and mild and yields of products **3** are satisfactory.

Acknowledgements

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Experimental

General

All reagents were commercially available. The 3,7-bis(*N,N*-dimethylamino)-10*H*-dibenz[b,e] iodinium iodide (**1**) was prepared according to the literature [8]. ^{1}H-NMR spectra were measured on a FC-80A spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were recorded for KBr pellets on a Nicolet 179SX FT-IR spectrophotometer. Mass spectra were determined on a HP-5988 AG CMS mass spectrometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

General Procedure for the Synthesis of Compounds **3a, 3b, 3d** *and* **3e**.

Compound **1** (506mg, 1 mmol), palladium acetate (0.02 mmol) and methanol (20 mL) were mixed under an argon atmosphere at room temperature. After adding Bu_3N (2 mmol), the inflow of argon was stopped and this gas was replaced with CO (1 atm) and the yellow suspension was stirred for 2h until a clear solution was obtained. The reaction was quenched with aqueous saturated NH_4Cl solution, then the mixture was extracted three times with Et_2O and the combined ether layers were dried over anhydrous $MgSO_4$. After evaporating the solvent, the crude product was separated by flash chromatography on silica gel using Et_2O and petroleum ether as eluents to give *methyl 2-[4'-(dimethylamino)- 2'-iodobenzyl]-4-dimethylaminobenzoate* (**3a**) as yellow crystals (355 mg, 81%); m.p. 91-92^{o}C; IR: ν = 3085, 1718, 1603, 1504, 583 cm^{-1}; ^{1}H-NMR: δ = 2.90 (s, 6H), 2.98 (s, 2H), 3.66 (s, 3H), 4.25 (s, 2H), 6.65-7.33 (m, 6H) ppm; MS: m/z = 438 (76) [M^+], 406 (22), 379 (14), 279 (76), 252 (28).

Similarly the following compounds were prepared:

Ethyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoate (**3b**). Yellow crystals (353 mg, 78%); m.p. 85-87 ^{o}C; IR: ν = 3075, 1713, 1602, 1500, 582 cm^{-1}; ^{1}H-NMR: δ = 0.94 (d, *J*=5.6 Hz, 3H), 2.79 (s, 6H), 2.88 (s, 6H), 4.16 (q, *J*=5.6Hz, 2H), 4.26 (s, 2H), 6.62 – 7.13 (m, 6H) ppm; MS: m/z = 452 (100) [M^{+}], 423 (19), 406 (39), 325 (72), 279 (88).

n-Propyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoate (**3d**). Yellow crystals (326 mg, 70%); m.p. 64-65 ^{o}C; IR: ν = 3075, 2964, 1713, 1605, 1504, 582 cm^{-1}; ^{1}H-NMR: δ = 1.00 (t, *J*=7.1 Hz, 3H), 1.79 (m, *J*=6.9 Hz, 2H), 2.91 (s, 6H), 2.98 (s, 6H), 4.26 (q, *J*=6.2 Hz, 4H), 6.66 – 7.36 (m, 6H) ppm; MS: m/z = 466 (100) [M^{+}], 423 (28), 406 (50), 339 (37), 279 (48), 452, 423 (19), 406 (39), 325 (72), 279 (88).

Diethylaminoethyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoate (**3e**). Viscous orange liquid (330 mg, 65%); IR: ν = 3020, 2967, 1715, 1604, 1504, 580, 443 cm^{-1}; ^{1}H-NMR: δ = 1.10 (t, *J*=7.1 Hz, 6H), 2.76 (m, 6H), 4.21 (s, 2H), 4.38 (t, *J*=6.3 Hz, 2H), 6.65 – 7.29 (m, 6H) ppm; MS: m/z = 523 [M^{+}] (59), 424 (86), 406 (50), 339 (13), 379 (13), 280 (100).

Synthesis of i-Propyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoate (**3c**).

Compound **1** (1 mmol), palladium acetate (0.02 mmol) and *iso*-propanol (20 mL) were mixed under an argon atmosphere at room temperature and then cooled in an ice bath. Sodium *iso*-propoxide (0.5 mmol) was added and the flask was allowed to warm up to room temperature, then the argon inflow was stopped and this gas was replaced with CO (1 atm.). The yellow suspension was stirred for 1h until a clear solution was formed and then the reaction was worked up as described for **3a** to give compound **3c** as a viscous yellow liquid (280 mg, 60%); IR: ν = 3072, 2980, 1709, 1603, 1502, 580 cm^{-1}; ^{1}H-NMR: δ = 1.27 (d, *J*=6.1 Hz, 6H), 2.89 (s, 6H), 2.97 (s, 6H), 4.23 (s, 2H), 4.74 (m, 1H), 6.52 – 7.30 (m, 6H) ppm; MS: m/z = 466 (100) [M^{+}], 423 (28), 406 (39), 339 (12), 279 (51).

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General Procedure for the Synthesis of Compounds **3f, 3g** and **3o.**

Compound **1** (1 mmol), palladium acetate (0.02 mmol), DMF (15 mL), Bu_3N (2 mmol) and *n*-propylamine (2 mmol) were added successively under an argon atmosphere and mixed at room temperature. The temperature was raised to 40^{o}C, the argon flow was stopped and this gas was replaced by CO (1 atm.) and stirring was continued until the yellow suspension turned into a clear solution. After reacting for 15 min. the reaction mixture was cooled to room temperature and worked up as described for **3a** to give *N-n-propyl-2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethyl-aminobenzoyl amide* (**3f**) as yellow crystals (419 mg, 90%); m.p. 139-140 ^{o}C; IR: ν = 1667, 1543 cm^{-1}; ^{1}H-NMR: δ = 0.96 (t, 3H), 1.58 (m, 2H), 2.89 (s, 6H), 2.97 (s, 6H), 3.32 (q, 2H), 4.09 (s, 2H), 6.65 (d, *J*=2.46 Hz, 1H), 6.73 (s, 1H), 6.86 (d, *J*=2.46 Hz, 1H), 6.94 (s, 1H), 7.20 (d, *J*=2.37 Hz, 1H), 7.33 (d, *J*=2.37 Hz, 1H) ppm; MS: m/z = 465 [M+] (8), 436 (60), 406 (19), 279 (100).

The following compounds were similarly prepared:

N-n-Butyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3g**). Yellow crystals; (434 mg, 91%); m.p. 118-120 ^{o}C; IR: ν = 1664, 1553 cm^{-1}; ^{1}H-NMR: δ = 0.96 – 1.03 (m, 3H), 1.23 – 1.67 (m, 4H), 2.90 (s, 6H), 2.97 (s, 6H), 3.25 – 3.55 (m, 2H), 4.08 (s, 2H), 6.65 (d, *J*=2.56 Hz, 1H), 6.73 (s, 1H), 6.87 (d, *J*=2.56 Hz, 1H), 6.94 (s, 1H), 7.20 (d, *J*=2.35 Hz, 1H), 7.33 (d, *J*=2.35 Hz, 1H) ppm; MS: m/z = 479 [M^{+}] (12), 436 (62), 406 (15), 279 (100).

N,N-Diethyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3o**). Yellow crystals (311 mg, 65%); m.p. 88-89 ^{o}C; IR: ν = 1675, 1637, 1603, 1504 cm^{-1}; ^{1}H-NMR: δ = 1.00 – 1.36 (m, 6H), 2.91 (s, 6H), 2.95 (s, 6H), 3.22 (q, 2H), 3.54 (q, 2H), 4.34 (s, 2H), 6.58 – 6.93 (m, 4H), 7.15 – 7.28 (m, 2H) ppm; MS: m/z = 479 [M^{+}] (10.8), 406 (85.8), 352 (17.1), 280 (91.9), 279 (100).

General Procedure for the Synthesis of Compounds **3h-3n**.

The method was as described for the preparation of **3f**, but *n*-propylamine was replaced by other amines, *i.e.* phenylamine (**2h**), *p*-methylphenylamine(**2i**), *m*-methylphenylamine (**2j**), *m*-ethoxy-phenylamine (**2k**), *o*-chlorophenylamine (**2l**), 2-aminobenzothiazole (2m), N-methylphenylamine (2 mmol) and the reaction temperature was 70 ^{o}C rather than 40 ^{o}C. In this manner the following compounds were prepared:

N-Phenyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3h**). Red crystals (444 mg, 89%); m.p. 197-198 ^{o}C; IR: ν = 1664, 1562 cm^{-1}; ^{1}H-NMR: δ = 2.94 (s, 6H), 2.96 (s, 6H), 4.34 (s, 2H), 6.76 – 7.59 (m, 11H) ppm; MS: m/z = 499 [M^{+}] (20), 406 (61.5), 279 (100).

N-p-Tolyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3i**). Red crystals (462 mg, 90%); m.p. 186-188 ^{o}C; IR: ν = 1664, 1594, 1564 cm^{-1}; ^{1}H-NMR: δ = 2.33 (s, 3H), 2.93 (s, 6H), 3.17 (s, 6H), 4.09 (s, 2H), 6.58 – 6.95 (m, 4H), 7.13 – 8.23 (m, 6H) ppm; MS: m/z = 513 [M^{+}] (2), 406 (10), 387 (16), 279 (95), 107 (100).

N-m-Tolyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3j**). Red crystals (446 mg, 87%); m.p. 155-157 ^{o}C; IR: ν = 1649, 1594, 1548 cm^{-1}; ^{1}H-NMR: δ = 2.35 (s, 3H), 2.92 (s, 6H), 2.98 (s, 6H), 4.08 (s, 2H), 6.66 – 6.96 (m, 4H), 7.07 – 7.47 (m, 6H) ppm; MS: m/z = 513 [M^{+}] (18), 406 (65), 386 (24), 279 (100).

N-m-Ethoxyphenyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3k**). Red crystals (445 mg, 82%); m.p. 120-122 ^{o}C; IR: ν = 1671, 1600, 1544 cm^{-1}; ^{1}H-NMR: δ = 1.33 (t, 3H), 2.90 (s, 6H), 3.10 (s, 6H), 4.06 (q, 2H), 4.18 (s, 2H), 6.59 – 7.29 (m, 6H), 7.51 – 8.23 (m, 4H) ppm; MS: m/z = 543 [M^{+}] (8.8), 417 (5), 406 (65), 279 (100).

N-o-Chlorophenyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3l**). Red crystals (427 mg, 80%); m.p. 124-125 ^{o}C; IR: ν = 1680, 1598, 1507 cm^{-1}; ^{1}H-NMR: δ = 2.89 (s, 6H), 2.99 (s, 6H), 4.15 (s, 2H), 6.56 – 7.55 (m, 8H), 7.96 (m, 1H), 8.55 (m, 1H) ppm; MS: m/z = 533 [M^{+}] (15), 534 [M^{+}+1] (5), 406 (72), 280 (100), 279 (72).

N-Benzothiazol-2-yl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3m**). Red crystals (378 mg, 68%); m.p. 108-109 ^{o}C; IR: ν = 1683, 1596, 1510 cm^{-1}; ^{1}H-NMR: δ = 2.90 (s, 6H), 3.05 (s, 6H), 4.28 (s, 2H), 6.53 – 7.33 (m, 6H), 7.45 – 8.40 (m, 4H) ppm. MS: m/z = 556 [M^{+}] (16), 406 (44), 280 (77), 279 (95), 133 (100).

N-Methyl-N-phenyl 2-[4'-(dimethylamino)-2'-iodobenzyl]-4-dimethylaminobenzoyl amide (**3n**). Red crystals (333 mg, 65%); m.p. 97-99 ^{o}C; IR: ν = 1644, 1598, 1510 cm^{-1}; ^{1}H-NMR: δ = 2.91 (s, 6H), 2.96 (s, 3H), 3.18 (s, 6H), 4.00 (s, 2H), 6.69 – 7.28 (m, 7H), 7.46 – 7.49 (m, 2H), 8.13 – 8.23 (m, 2H) ppm; MS: m/z = 513 [M^{+}] (2), 406 (62.5), 279 (100).

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