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Ionic-Liquid-Promoted Palladium-Catalyzed Multicomponent Cyclocarbonylation of *o*-Iodoanilines and Allenes To Form Methylene-2,3-dihydro-1*H*-quinolin-4-ones

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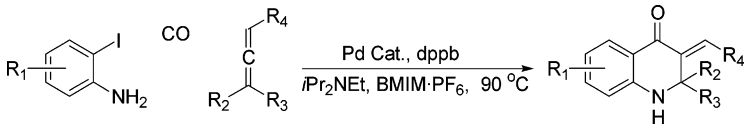

The palladium-catalyzed cyclocarbonylation reaction of *o*-iodoanilines with allenes and CO in 1-butyl-3-methylimidazolium hexafluorophosphate afforded 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones in moderate to excellent yields under a low pressure (5 atm) of CO. The ionic liquid, as the solvent and promoter, enhances the efficiency of the cyclocarbonylation reaction. The recyclability of the system of ionic liquid/catalyst/ligand was also demonstrated.

Introduction

2,3-Dihydro-1*H*-quinolin-4-ones are of considerable interest due to their pharmacological properties,[1] e.g., as antimitotic agents.[2] Moreover, they are valuable precursors[3] for the synthesis of medicinally important compounds such as nonsteroidal androgen receptor agonists,[4] the antimalarial drug chloroquine,[5] and martinellines with antibacterial activity.[6] Various synthetic methods have been reported for the synthesis of 2,3-dihydro-1*H*-quinolin-4-ones.[7] The cyclization of 2′-aminochalcones or 3-(substituted anilino)propionic acid is a widely used pathway. The solid-phase synthesis of 2,3-dihydro-1*H*-quinolin-4-ones has also been reported recently.[8] Most of these processes often suffer from multistep procedures, low yields, or the need for a large amount of catalyst. The direct preparation of 2,3-dihydro-1*H*-quinolin-4-ones has received relatively little attention.[7a,e,k] Thus, it is desirable to develop a straightforward and efficient method to synthesize these compounds.

Transition-metal-complex-catalyzed multicomponent reactions are powerful methods for organic synthesis,[9] because the formation of several carbon−carbon and/or carbon−heteroatom bonds and the assembly of complex molecular structures can occur from simple starting materials in a one-pot reaction. Transition-metal-complex-catalyzed cyclocarbonylation reac-

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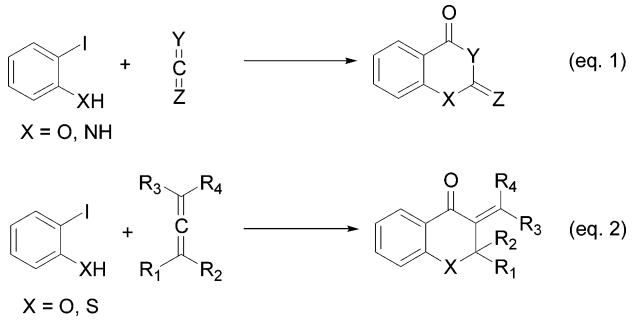
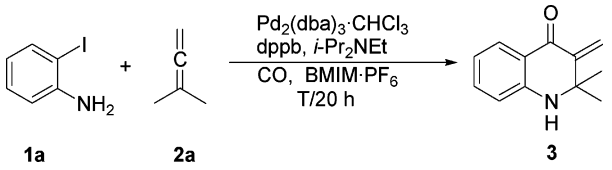
SCHEME 1



tions are among the most useful processes for directly creating heterocycles.[10] Examples of palladium-catalyzed carbonylation of *o*-phenols and *o*-iodoanilines with alkynes,[11] norbornene,[12] and allenes[13] have been reported. We recently accomplished the preparation of benz[*e*]-1,3-oxazin-4-ones[14] and 4(3*H*)-quinazolinone derivatives[15] from *o*-iodophenols or *o*-iodoanilines with heterocumulenes and carbon monoxide using palladium catalysts in classical organic solvents (Scheme 1, eq 1). We also reported the palladium-catalyzed carbonylation of *o*-iodophenols or *o*-iodothiophenols with allenes under high pressure to form 2,3-dihydro-4*H*-1-benzopyran-4-one[16] and thiochroman-4-ones,[17] respectively (Scheme 1, eq 2).

To the best of our knowledge, there have been no reports on the direct cyclocarbonylation reaction of *o*-iodoanilines with allenes. It is conceivable that the nucleophilicity of the amino group prevents the success of the reaction. Indeed, the protection of the amino group by strongly electron-withdrawing groups such as acetyl, tosyl, and trifluoroacetyl was often used to alleviate the problem in similar reactions.[7f,k,11a,d] It is well-known that ionic liquids,[18] which have been widely used as environmentally benign reaction media, can enhance reaction yields

SCHEME 2



and rates for a number of reactions.[19] Recently, we reported that the cyclocarbonylation of unsaturated phenols and anilines, catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ in an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM·PF_6), provided lactones or lactams in fine yields, selectivities, and recyclability.[20] We also found the BMIM·PF_6 could improve the efficiency of the cyclocarbonylation of 3-phenyl-1-propynes with iodoarenes to form (*E*)-3-arylidenebutenolides using $Pd_2(dba)_3{\cdot}CHCl_3$ as the catalyst under moderate conditions.[21] These results encouraged us to investigate the cyclocarbonylation of *o*-iodoanilines with allenes to give 2,3-dihydroquinolin-4(1*H*)-ones in an ionic liquid; the latter might also enhance the efficiency of the process. We report the first examples of the directed synthesis by palladium-catalyzed multicomponent cyclocarbonylation of *o*-iodoanilines with allenes and CO and the improvement of this process by an ionic liquid. The recyclability of the ionic liquid containing the palladium catalyst and ligand was also investigated.

Results and Discussion

Initially, we chose the cyclocarbonylation of *o*-iodoaniline (**1a**) and 3-methyl-1,2-butadiene (**2a**) as the model reaction (Scheme 2). The system of BMIM·PF_6 and $Pd_2(dba)_3{\cdot}CHCl_3$, used previously for the cyclocarbonylation of phenols and anilines,[20] and the reaction of 3-phenyl-1-propynes with iodoarenes and CO,[21] was employed for the present reaction. Treatment of *o*-iodoaniline (0.5 mmol) and 3-methyl-1,2-butadiene (1.0 mmol) with 20 atm of carbon monoxide and diisopropylethylamine (1.0 mmol) in the presence of a catalytic

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TABLE 1. Cyclocarbonylation Reaction of *o*-Iodoaniline and 3-Methyl-1,2-butadiene under Different Conditions[a]

entry	catalyst (amount, mol %)	solvent	CO pressure (atm)	*T* (°C)	yield[b] (%)
1[c]	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	BMIM·PF_6	20	90	49
2[c]	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	BMIM·PF_6	20	35	NR[d]
3[c]	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	BMIM·PF_6	20	60	22
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·PF_6	20	90	63
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·BF_4	20	90	58
6	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·NTf_2	20	90	34
7	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·PF_6	6.8	90	75
8	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·PF_6	5	90	74
9	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·PF_6	5	90	67[e]
10	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·PF_6	3	90	58
11	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	BMIM·PF_6	5	90	53[f]
12	Pd $(OAc)_2$ (2)	BMIM·PF_6	20	90	25
13	Pd $(PPh_3)_4$ (2)	BMIM·PF_6	5	90	20
14	Pd $(PPh_3)_2Cl_2$ (2)	BMIM·PF_6	5	90	24
15	$Pd_2(dba)_3{\cdot}HCl_3$ (2)	C_6H_6	5	90	37[g]

[a] Reaction conditions: *o*-iodoaniline (0.5 mmol), 3-methyl-1,2-butadiene (1.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol), dppb (0.01 mmol), *i*-Pr_2NEt (1.0 mmol), ionic liquid (2.5 g), reaction time 20 h. [b] Isolated yield. [c] dppb (5 mol %). [d] No reaction. [e] dppf (0.01 mmol) was used instead of dppb. [f] Scale: 5 mmol of *o*-iodoaniline. [g] C_6H_6 (3 mL).

amount of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %) and 1,4-bis(diphenylphosphino)butane (dppb; 5 mol %) in BMIM·PF_6 at 90 °C for 20 h resulted in the formation of 2,2-dimethyl-3-methylene-2,3-dihydro-1*H*-quinolin-4-one (**3**) in 49% yield (Table 1, entry 1). At lower temperature, the reaction did not occur or only gave the desired product in low conversion and reduced yield (Table 1, entries 2 and 3). When 2 mol % catalyst and ligand were used, the cyclocarbonylation reaction proceeded cleanly and gave a higher yield of **3** (Table 1, entry 4). The optimal pressure of CO for the cyclocarbonylation reaction is 5.0−6.8 atm (Table 1, entries 7 and 8). Lower product yields were obtained using BMIM·BF_4 or BMIM·NTf_2 instead of BMIM·PF_6 (Table 1, entries 5 and 6). 1,1-Bis(diphenylphosphino)-ferrocene (dppf) could also be used for this process, affording a comparable yield of the desired product **3** (Table 1, entry 9). The utilization of other catalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$ was not beneficial for the reaction, giving much lower yields of **3** (Table 1, entries 12−14). The optimized conditions, involving the use of 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and dppb under 5 atm of CO in BMIM·PF_6 at 90 °C for 20 h, were employed for the cyclocarbonylation of *o*-iodoaniline with 3-methyl-1,2-butadiene, affording **3** in 74% yield (Table 1, entry 8). Using the latter conditions, but effecting the reaction on a 5 mmol (rather than 0.5 mmol) scale of *o*-iodoaniline, gave **3** in good yield (Table 1, entry 11). The beneficial effect of BMIM·PF_6 as a solvent was demonstrated by comparison with the result using benzene, as the yield of **3** is only 37% using C_6H_6 (Table 1, entry 15) compared with 74% in the ionic liquid (Table 1, entry 8). The reaction could be performed under a low pressure of CO in BMIM·PF_6, while a high pressure of CO is often required for cylcocarbonylation in a conventional organic solvent.[14−17]

The optimized reaction conditions described in Table 1, entry 8, were used to determine the scope and limitations of the cyclocarbonylation reaction of *o*-iodoanilines with allenes. A variety of 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones could be synthesized in moderate to excellent yields under these conditions. Note that 2 equiv of allenes was employed since lower product yields resulted if only 1 equiv of an allene was used. The reactions of substituted *o*-iodoanilines **1b**−**1e** with allenes and carbon monoxide proceeded successfully and gave the desired 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones in fine yields, while a complicated mixture was obtained when the *o*-iodoanilines had strongly electron-withdrawing groups such as 4-cyano-2-iodoaniline and 2-iodo-4-nitroaniline (Table 2). The terminal disubstituted allenes **2a**−**2c** reacted with *o*-iodoanilines and CO, affording the corresponding 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones in 52−90% yields. It is interesting to note that the allylic substitution reaction occurred at the more substituted allenic terminal cation, which is consistent with the palladium-catalyzed carbonylation of functionally substituted aryl halides with allenes and its unsymmetrical as well as carbonylative versions.[16,17,22] 1,2-Cyclononadiene (**2d**) reacted in an analogous manner with the terminal disubstituted allenes, giving the expected 5,5a,6,7,8,9,10,11-octahydro-5-azacyclonona[*b*]naphthalen-13-ones **13**−**15** in 60−71% yields, while the cyclocarbonylation of the symmetrical internal acyclic diene **2e** resulted in the formation of a mixture of the desired product and isomers in 85% yield. When unsymmetrical allene **2f** was used as the reactant, 3-styryl-2,3-dihydro-1*H*-quinolin-4-one (**17a**) was obtained in 63% yield as the major product with a 9% yield of isomer **17b**. 1-Phenyl-1,2-butadiene (**2g**) gave results similar to those of allene **2f** even if it was a phenyl group which could decrease the reactivity of the corresponding C−C double bond due to its conjugation. The electron-poor allene ethyl 2,3-pentadienecarboxylate is less reactive than other allenes with ethyl (2-methyl-4-oxo-1,4-dihydro-2*H*-quinolin-3-ylidene)carboxylate (**19**) formed in 21% yield.

The recyclability of the ionic liquid containing the palladium catalyst and ligand was now investigated (see Table 3 for the results). After completion of the first run, the product was isolated by simple extraction with diethyl ether. Fresh *o*-iodoaniline, allene, and diisopropylethylamine were added to the remaining ionic liquid for the next run. Attempted use of the catalyst species recovered from the first run gave product **3** in only 37% yield, which indicates the deterioration of the catalyst (Table 3, entry 2). To prevent the problem, more dppb was employed. As expected, the system of ionic liquid, palladium catalyst, and dppb could be recovered and reused 4−6 times without a significant decrease in the yield when 4 mol % dppb was used.

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TABLE 2. Cyclocarbonylation Reaction of *o*-Iodoanilines and Allenes[a]

entry	aniline	allene	product	yield(%)[b]
1	**1a**	**2a**	**3**	74
2	**1b**	**2a**	**4**	67
3	**1c**	**2a**	**5**	84
4	**1d**	**2a**	**6**	56
5	**1e**	**2a**	**7**	52
6	**1a**	**2b**	**8**	72
7	**1b**	**2b**	**9**	90
8	**1c**	**2b**	**10**	82
9	**1e**	**2b**	**11**	58
10	**1a**	**2c**	**12**	80
11	**1a**	**2d**	**13**	66
12	**1b**	**2d**	**14**	71
13	**1d**	**2d**	**15**	60[c]
14	**1a**	**2e**	**16a**(52%) **16b**(33%)	85
15	**1a**	**2f**	**17a**(63%) **17b**(9%)	72
16	**1a**	**2g**	**18a**(55%) **18b**(29%)	84
17	**1a**	**2h**	**19**	21

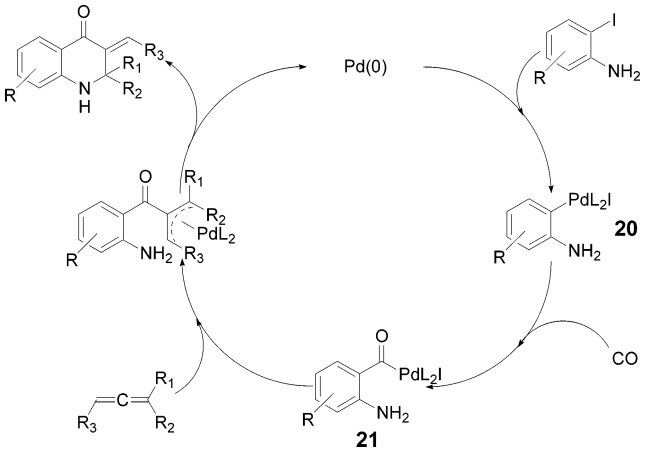
[a] Reaction conditions: *o*-iodoaniline (0.5 mmol), allene (1.0 mmol), CO (5 atm), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol), dppb (0.01 mmol), *i*-Pr_2NEt (1.0 mmol), BMIM·PF_6 (2.5 g), temperature 90 °C, reaction time 20 h. [b] Isolated yield. [c] 120 °C/20 h.

TABLE 3. Recyclability of the Ionic Liquid Containing a Palladium Catalyst[a]

entry	aniline	allene	dppb	Run	time (h)	yield(%)[b]
1			2% mol	1	20	74
2				2	24	37
3			4% mol	1	20	66
4				2	24	68
5				3	36	66
6				4	48	70
7				5	48	62
8				6	48	53
9				1	48	64
10			4% mol	1	20	76
11				2	35	71
12				3	48	69
13				4	48	41

[a] Reaction conditions: (first run) *o*-iodoaniline (0.5 mmol), allene (1.0 mmol), CO (5 atm), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.01 mmol), *i*-Pr_2NEt (1.0 mmol), BMIM·PF_6 (2.5 g), temperature 90 °C, reaction time 20 h; (next runs) *o*-iodoaniline (0.5 mmol), allene (1.0 mmol), *i*-Pr_2NEt (1.0 mmol). [b] Isolated yield.

SCHEME 3



A possible mechanism for the cyclocarbonylation of *o*-iodoanilines with allenes is outlined in Scheme 3. The oxidative addition of the palladium species to an iodoaniline generates **20**, which undergoes CO insertion to form the acylpalladium intermediate **21**. The addition of acylpallladium intermediate **21** to the allene can give a π-allylpalladium species, which then can be subjected to nucleophilic attack by the amino group followed by reductive elimination to give the product and regenerate the catalyst.

In conclusion, the direct cyclocarbonylation reaction of *o*-iodoanilines and allenes proceeds smoothly in BMIM·PF_6 under a low pressure of CO to form 3-methylene-2,3-dihydro-1*H*-quinolin-4-ones. The ionic liquid enhanced the reactivity of *o*-iodoanilines, both as a solvent and as a reaction promoter. The system is recyclable.

Experimental Section

Representative Procedure for the Cyclocarbonylation Reaction. A mixture of 2-iodo-4-methylaniline (**1b**; 117 mg, 0.5 mmol), vinylidenecyclohexane (**2b**; 108 mg, 1.0 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$

(10 mg, 0.01 mmol), 1,4-bis(diphenylphosphino)butane (4.3 mg, 0.01 mmol), diisopropylethylamine (0.17 mL, 1.0 mmol), and BMIM·PF_6 (2.5 g) was charged in a 45 mL autoclave. The autoclave was purged, pressurized with CO (5 atm), and stirred at 90 °C for 20 h. The reaction was cooled to room temperature and extracted with diethyl ether. The solvent was removed by rotary evaporation, and the residue was subjected to short flash column chromatography using a 1/3 mixture of ethyl acetate and hexane as the eluant, affording 104 mg (90%) of **9**. IR (neat): 3358 (NH), 1683 (C═O), 1651 (C═C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23−1.33 (m, 1H), 1.40−1.61 (m, 4H), 1.66−1.71 (m, 3H), 2.00 (d, J = 12.0 Hz, 2H), 2.24 (s, 3H), 4.57 (s, 1H), 5.44 (s, 1H), 6.21 (s, 1H), 6.59 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 21.5, 25.0, 34.4, 56.8, 116.0, 118.1, 118.7, 127.2, 127.6, 136.7, 147.4, 149.9, 184.6. HRMS (EI): *m*/*z* calcd for $C_{16}H_{19}NO$ 241.1467, found 241.1475.

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Supporting Information Available: General procedure for the synthesis of 3-methylene-2,3-dihydro-1*H*-quinilin-4-ones **3**−**19** and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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