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Synthesis of 2-Quinolones via Palladium-Catalyzed Carbonylative Annulation of Internal Alkynes by *N*-Substituted *o*-Iodoanilines

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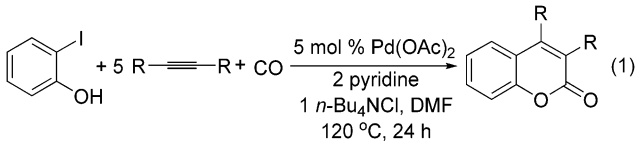
The palladium-catalyzed annulation of internal alkynes by *N*-substituted *o*-iodoanilines under 1 atm of carbon monoxide results in the formation of 3,4-disubstituted 2-quinolones. The nature of the substituent on the nitrogen is crucial to obtaining high yields of 2-quinolones. The best results are obtained using alkoxycarbonyl, *p*-tolylsulfonyl, and trifluoroacetyl substituents. The nitrogen substituent is lost during the course of the reaction resulting in the formation of *N*-unsubstituted 2-quinolones. A variety of internal alkynes, bearing alkyl, aryl, heteroaryl, hydroxyl, and alkoxyl substituents, are effective in this process. Electron-rich and electron-poor *N*-substituted *o*-iodoanilines, as well as heterocyclic analogues, can be employed as annulating agents.

Introduction

In the last two decades, the development of transition-metal-catalyzed multicomponent processes, which involve the formation of several carbon−carbon and/or carbon−heteroatom bonds, has significantly expanded the arsenal of synthetic organic chemistry, allowing easy access to complex molecular structures from fairly simple precursors. In particular, palladium-catalyzed annulations of unsaturated molecules, such as 1,3-dienes, allenes, and internal alkynes, with various functionally substituted aryl and vinylic halides provide a concise and efficient route to a wide variety of hetero- and carbocycles.[1] The introduction of an additional component, such as carbon monoxide, into these processes would further increase their efficiency and synthetic utility. Several examples of palladium-catalyzed reactions of *o*-iodophenols and *o*-iodoanilines with norbornene,[2] norbornadiene,[3] allenes,[4] and terminal alkynes[3a,5] in the presence of CO have been reported.

We have recently reported that the palladium-catalyzed carbonylative annulation of internal alkynes with *o*-iodophenols results in the exclusive formation of coumarins (eq 1).[6] This process exhibits a unique reactivity,



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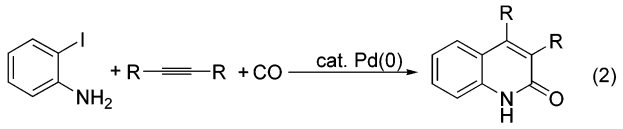
namely the intermolecular insertion of an internal alkyne into an arylpalladium bond in preference to the insertion of CO. We envisioned that this process might be extended to *o*-iodoanilines, which would lead to the formation of 3,4-disubstituted 2-quinolones (eq 2).



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The 2-quinolone core is widely found in various alkaloids, many of which possess interesting biological activity. There has been considerable interest in developing 2-quinolones as anticancer,[7] antiviral,[8] and antihypertensive agents.[8] 4-Substituted 3-phenyl-2-quinolones exhibit high affinity in binding to the glycine site of the *N*-methyl-D-aspartate receptor, and such antagonists have promise for the treatment of several central nervous system disorders.[9] Amides of 3-hydroxy- and 3-alkyl-4-carboxylic acids of 2-quinolones also exhibit high affinity for the 5-HT_3 serotonin receptor.[10] 2-Quinolones are also valuable intermediates in organic synthesis, since they

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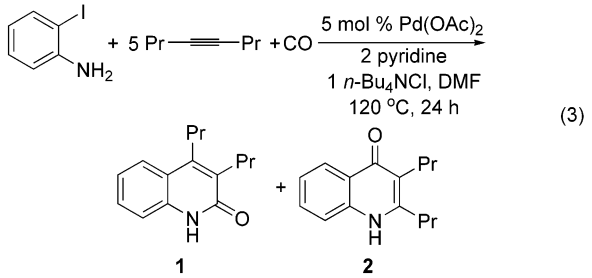
are easily converted into 2-chloro- and then 2-aminoquinoline derivatives.[11]

The classic methods of synthesis of 2-quinolones include a base-catalyzed intramolecular aldol condensation leading to formation of the C3−C4 bond (the Friedländer synthesis[12] and the Camps modification of the Friedländer synthesis[13]) and an acid-catalyzed cyclization of *β*-ketoanilides forming the C9−C4 bond (the Knorr synthesis[14]). While a wide variety of 3- or 4-substituted 2-quinolones can be synthesized using these methods, the utility of these reactions for the synthesis of 3,4-disubstituted 2-quinolones is quite limited.[15] Several other methods for the synthesis of 3,4-disubstituted 2-quinolones, such as the titanium-promoted intramolecular reductive cyclization of *N*-(2-acylphenyl) α-ketoamides,[16] the $AlCl_3$-promoted annulation of terminal and internal alkynes,[17] and the electrocyclic closure of 2-isocyanatostyrenes generated in situ by oxidation of the corresponding 2-cyanostyrenes with *m*-CPBA,[18] have been reported. The yields of these processes, however, are often low, and the variety of substrates is very limited. Very few examples of the palladium-catalyzed synthesis of 2-quinolones have been reported, and the utility of these processes is again severely limited. Two of these methods are based on the Heck reaction of 2-iodoanilines[19] or 2-bromonitrobenzenes[20] with *β*-substituted acrylic acids, followed by intramolecular cyclization, and another method involves the intramolecular carbonylation of (*Z*)-2-acetamino-α-bromostyrene.[21]

Herein, we report a new method for the synthesis of 2-quinolones via palladium-catalyzed carbonylative annulation of internal alkynes by *N*-substituted *o*-iodoanilines.

Results and Discussion

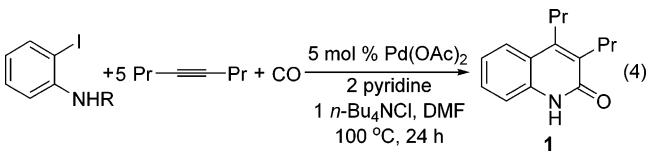
Optimization of the Reaction Conditions. Application of our standard reaction conditions for the synthesis of coumarins to the reaction of *o*-iodoaniline and various internal alkynes, such as 4-octyne and diphenylacetylene, in the presence of 1 atm of CO afforded neither the desired 2-quinolone product **1** nor the isomeric 4-quinolone **2** (eq 3). Variations of the palladium catalyst, the



(3)

base, and the temperature or the addition of phosphine ligands did not result in any improvement. In some of these reactions, we isolated small amounts of byproducts apparently arising from the attack of the amino group of 2-iodoaniline on the acylpalladium complex formed from another molecule of 2-iodoaniline. Thus, we speculate that the failure of the annulation process can be attributed to the high nucleophilicity of the amino group. Therefore, protection of the amino group was explored as a possible strategy to alleviate the problem. Indeed, the reaction of 4-octyne with *N*-tosyl-*o*-iodoaniline under the standard coumarin reaction conditions afforded 3,4-dipropyl-2-quinolone (**1**) in a 56% yield. Unexpectedly, the tosyl group was removed during the course of the reaction, and no traces of the quinolone containing the tosyl group were detected. The same yield of 2-quinolone **1** was obtained when the reaction was run at 100 °C, though it required 48 h to reach completion.

Encouraged by our initial success, we examined the effect of a variety of protecting groups on this process (eq 4 and Table 1), including an alkyl (entry 2), sulfonyl (entries 3, 7, and 8), acyl (entries 4, 6, and 9), aminocarbonyl (entry 5), and alkoxycarbonyl groups (entries 10 and 11). None of the desired product was obtained when



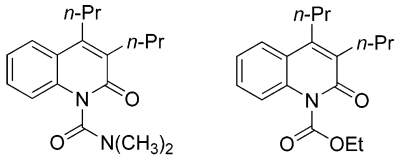
(4)

a simple alkyl substituent was employed (entry 2). Only the reduction product, *N*-methylaniline, was isolated in a 33% yield, along with 26% of the unreacted starting material. Analysis of the results with other substituents (entries 3−11) shows that the yield of quinolone **1** depends on the electron-withdrawing ability of the substituent on the nitrogen, as measured by the pK_a (NH)

TABLE 1. Effect of the Substituent on the Nitrogen (eq 4)[a]

entry	R	% yield of **1**	% recovery of starting material
1	H	0	
2	CH_3	0[b]	26
3	SO_2CF_3	traces	55
4	$COCH_3$	12	12
5	$CON(CH_3)_2$	23[c]	0
6	CHO	33	0
7	SO_2CH_3	40	20
8	SO_2-*p*-Tol	56[d]	0
9	$COCF_3$	56	0
10	$CO_2CH_2CH_3$	71[e]	0
11	$CO_2C(CH_3)_3$	75	0

[a] Standard reaction conditions: *N*-substituted *o*-iodoaniline (0.5 mmol), 4-octyne (2.5 mmol), pyridine (1 mmol), *n*-Bu_4NCl (0.5 mmol), and $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 mL) at 100 °C for 24 h. [b] *N*-Methylaniline was isolated in 33% yield. [c] Isolated as a 70:30 mixture of **1** and **3**. [d] The reaction was run for 48 h. [e] Isolated as an 85:15 mixture of **1** and **4**.



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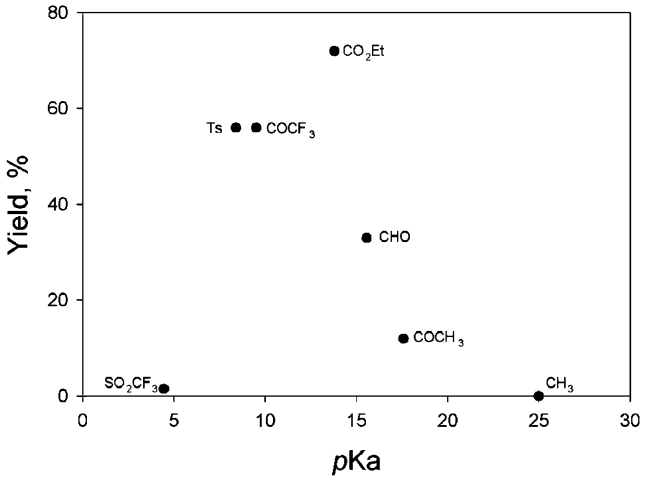
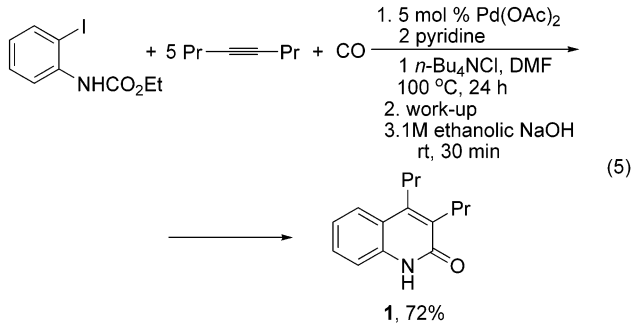


FIGURE 1. Dependence of the yield of **1** on the pK_a (NH) of PhNHR (the R group is shown next to the data points).

of the corresponding *N*-substituted anilines[22] (Figure 1). High yields of the quinolone were obtained when strongly electron-withdrawing groups, such as tosyl or trifluoroacetyl, are employed (entries 8 and 9), while the use of weaker electron-withdrawing groups, such as an acetyl group (entry 4), results in a significant decrease in the yield. It is worth noting that the pK_a's of *N*-tosylaniline (8.40) and trifluoroacetanilide (9.51) are close to the pK_a of phenol (9.98). Therefore, the effect of the electron-withdrawing strength of the nitrogen substituent likely indicates that deprotonation of the NH group occurs during the reaction. The best results, however, have been obtained by employing alkoxycarbonyl substituents (entries 10 and 11), even though these groups are not as strong electron-withdrawing groups as tosyl or trifluoroacetyl (pK_a for $PhNHCO_2Et$ = 13.8, Figure 1). Moreover, the reaction of an *o*-iodoaniline bearing an extremely strong electron-withdrawing group, such as trifluoromethanesulfonyl (entry 3), did not afford any of the desired product. Due to its high acidity (pK_a = 4.55), the *N*-(2-iodophenyl)trifluoromethanesulfonamide is probably significantly deprotonated under the reaction conditions (pK_a of pyridine is 5.20), and the anionic species is apparently completely inactive in the annulation reactions. Thus, a variety of factors determines the suitability of the protecting group, and careful selection of such a group is paramount for the success of the reaction.

It should be mentioned here that the reactions of all but two *N*-substituted *o*-iodoanilines shown in Table 1 afforded only the unprotected quinolone **1**. The in situ deprotection of the 2-quinolone nitrogen is not unprecendented. Bolotin and co-workers reported that the condensation of *N*-tosyl-2-aminobenzaldehyde with phenylacetic acid afforded only unprotected 3-phenyl-2-(1*H*)-quinolone in a 90% yield.[23] Similarly, the palladium-catalyzed carbonylation of *Z*-2-acetamino-α-bromostyrene also produced only the unprotected 2-quinolone.[21]

In our studies, only in the reactions of *N*,*N*-dimethyl-*N*′-(2-iodophenyl)urea (entry 5) and ethyl *N*-(2-iodophenyl)carbamate (entry 10) was the protected quinolone isolated in 7% and 11% yields, respectively. Since the reaction with ethyl *N*-(2-iodophenyl)carbamate afforded one of the best yields of the desired product, ways to achieve complete deprotection during the reaction have been explored. Increasing the amount of pyridine to 5 equiv did not produce the desired result; the yields of **1** and **4** were 47% and 18%, respectively. Increasing the temperature to 120 °C led to the disappearance of **4**, but the yield of **1** was only 57%. While variation of the reaction conditions did not succeed in getting rid of **4**, compound **4** can be readily converted to **1** by treatment with 1 M ethanolic NaOH for 30 min at room temperature. When the entire reaction mixture from the annulation of 4-octyne was treated with 1 M ethanolic NaOH, quinolone **1** was obtained in a 72% yield (eq 5). As



(5)

indicated in Table 1, the unprotected product **1** can be obtained as the only product in a 75% yield by employing *tert*-butyl *N*-(2-iodophenyl)carbamate (entry 11). Although this higher yield using a simpler procedure makes the *tert*-butyl carbamate appear to be the protecting group of choice, in most of our studies the ethyl carbamate moiety was employed because it is easier to prepare and handle (ethyl *N*-(2-iodophenyl)carbamate is a solid, while the *tert*-butyl carbamate is a viscous liquid).

The effects of the palladium catalyst, the base, the chloride source, the stoichiometry of the reactants, the reaction time, and the temperature were next examined using *N*-ethoxycarbonyl and *N*-tosyl derivatives of 2-iodoaniline. The results of this study are summarized in Table 2.

First, various palladium catalysts have been evaluated. It can be seen from the results that $Pd(OAc)_2$ and $Pd(dba)_2$ are generally equally effective in this process (compare entries 1 and 2, and 6 and 7). Surprisingly, palladium complexes containing phosphine ligands are completely ineffective in the reactions with ethyl *N*-(2-iodophenyl)carbamate (entries 3−5). Even the simple

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TABLE 2. Effect of the Palladium Catalyst on the Yield of Quinolone 1 (eq 4)[a]

entry	R	catalyst	base	% yield[b]
1	CO_2Et	$Pd(OAc)_2$	pyridine	71 (85:15)
2		$Pd(dba)_2$		66 (86:14)
3		$Pd(PCy_3)_2$		13 (62:38)
4		$Pd(OAc)_2 + 2PPh_3$		6
5		$Pd(PPh_3)_4$		2
6	Ts	$Pd(OAc)_2$	pyridine	56
7		$Pd(dba)_2$		56
8		$Pd(OAc)_2 + 2PPh_3$		50
9		$Pd(OAc)_2$	NaOAc	0
10			NEt_3	22[c]
11	CO_2Et		NEt_3	37[d]
12			pyridine[e]	66 (76:24)
13			pyridine[f]	72 (86:14)

[a] Standard reaction conditions: *N*-substituted *o*-iodoaniline (0.5 mmol), 4-octyne (2.5 mmol), pyridine (1 mmol), *n*-Bu_4NCl (0.5 mmol), and Pd catalyst (5 mol %, 0.025 mmol) with or without PPh_3 (10 mol %, 0.05 mmol) under 1 atm of CO in DMF (5 mL) at 100 °C for 24 h. [b] The ratio of **1**/**4** is given in parentheses. [c] *N*-Tosyl-2,3-dipropylindole was obtained in a 43% yield. [d] *N*-Ethoxycarbonyl-2,3-dipropylindole was obtained in a 15% yield. [e] No chloride source was added. [f] 1 equiv of LiCl was used as a chloride source.

addition of 10 mol % of triphenylphosphine to the reaction mixture results in almost complete suppression of the reaction (entry 4). This dramatic effect, however, is not observed in the reactions with the tosylamide derivative; a 50% yield of **1** was obtained when 10 mol % of PPh_3 was employed (entry 8).

The use of pyridine as a base was crucial for the success of our coumarin synthesis.[6] Therefore, several bases have also been examined to determine if this is true for this process as well (entries 9−11). None of the desired quinolone **1** was detected in the reaction of the tosylamide derivative when the inorganic base NaOAc was used (entry 9). The use of triethylamine, in the reactions with either the *N*-tosyl or *N*-ethoxycarbonyl derivative, resulted in low yields of **1** (entries 10 and 11). Moreover, the use of triethylamine leads to the formation of significant amounts of 2,3-dipropylindole derivatives. This is likely because NEt_3 is a much stronger base than pyridine, and it apparently deprotonates the amino group much more easily, especially when a strong electron-withdrawing substituent like a tosyl group is employed. Thus, in the vinylpalladium complex formed after insertion of the alkyne, the palladium atom is strongly coordinated by the nitrogen atom, and reductive elimination leading to formation of the indole occurs faster than the insertion of CO. Note that no deprotection of the indole nitrogen occurs during the reaction. A small amount of the protected quinolone **4** (about 5%) has also been detected in the reaction of ethyl *N*-(2-iodophenyl)-carbamate with Et_3N as the base.

Elimination of the chloride source from the reaction mixture slightly reduces the yield of the quinolone **1** (66%, entry 12), while the use of a different chloride salt, LiCl (entry 13), gave virtually the same result as the use of *n*-Bu_4NCl (72% and 71%, respectively).

Next, the reaction temperature and time were varied to find the optimal conditions. The results are summarized in Table 3. *N*-(2-Iodophenyl)tosylamide is considerably less reactive than ethyl *N*-(2-iodophenyl)carbamate, and the reactions of the sulfonamide derivatives

TABLE 3. Effect of the Reaction Time and Temperature[a]

entry	R	*T* (°C)	time (h)	% yield of **1**[b]
1	Ts	80	48	30
2		100	24	42
3			48	56
4		120	12	47
5			24	56
6	CO_2Et[a]	80	12	37 (8:92)
7			24	52 (19:81)
8		100	6	71 (41:59)
9			12	75 (69:31)
10			24	71 (85:15)
11		120	24	57 (100:0)

[a] Standard reaction conditions: *N*-substituted *o*-iodoaniline (0.5 mmol), 4-octyne (2.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol), pyridine (1 mmol), and *n*-Bu_4NCl (0.5 mmol) under 1 atm of CO in DMF (5 mL). [b] Ratio of **1**/**4** in parentheses.

need to be run at 120 °C to reach completion in 24 h (entries 1−5). On the other hand, the annulation is complete after 6 h at 100 °C, when ethyl *N*-(2-iodophenyl)carbamate is employed. However, the major product after 6 h is the protected quinolone **4**. This compound is hydrolyzed to **1** fairly slowly under the reaction conditions, and the hydrolysis is incomplete even after 24 h at 100 °C. At higher temperatures (120 °C), the carbamate affords only **1** after 24 h, but the yield is considerably lower (entry 11). At lower temperatures (80 °C), the carbonylative annulation is notably slower. The reaction requires 24 h to reach completion, and even in this case the overall yield is only 52% (entries 6 and 7). Interestingly, little deprotection occurs at 80 °C.

Scope and Limitations. The carbonylative annulation of various internal alkynes with ethyl *N*-(2-iodophenyl)carbamate was subsequently examined to determine the scope and limitations of this reaction. The reactions were run under the following "optimized" conditions: 0.5 mmol of the 2-iodoaniline carbamate derivative, 5 mol % $Pd(OAc)_2$, 2 equiv of pyridine, and 1 equiv of *n*-Bu_4NCl in 5 mL of DMF at 100 °C for 12 h. The crude products were treated for 30 min at room temperature with 1 M ethanolic NaOH to complete the hydrolysis of the carbamate protecting group. The results of this study are summarized in Table 4.

The carbonylative annulation of dialkyl (entries 1−5), as well as alkylaryl acetylenes (entries 6−9), affords the desired quinolones in 56−82% yields. These yields are comparable or slightly better than the yields of the corresponding coumarins (for example, with 4-octyne 71% vs 63% and with 1-phenyl-1-butyne 82% vs 78%, respectively). Moreover, no significant decrease in the yield of the quinolones is observed when the amount of the internal alkyne is reduced to 3 equiv (compare entries 1 and 2, 4 and 5, and 6 and 7). Even the use of only 2 equiv of 4-octyne in the reaction with ethyl *N*-(2-iodophenyl)-carbamate afforded 2-quinolone **1** in a satisfactory yield (entry 3). The carbonylative annulation of 1-phenyl-1-propyne (entry 8) and 1-(2-methoxyphenyl)-1-butyne (entry 9) employing 3 equiv of the alkynes also afforded the desired quinolones in good yields.

The limitations of the process are similar to those of the coumarin synthesis. The annulation of unsymmetrical alkynes, such as 1-phenyl-1-butyne, produces mixtures of regioisomers, which arise from the two possible

TABLE 4. Synthesis of 3,4-Disubstituted 2-Quinolones via Palladium-Catalyzed Annulation of Internal Alkynes[a]

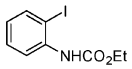
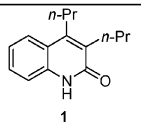
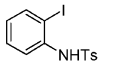
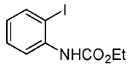
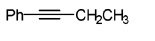
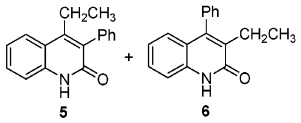
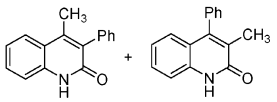
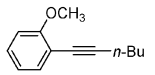
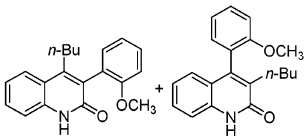
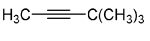
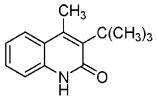
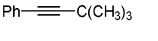
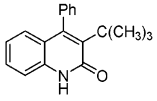
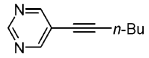
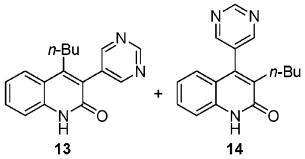
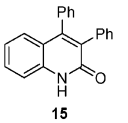
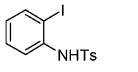
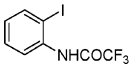
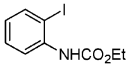
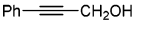
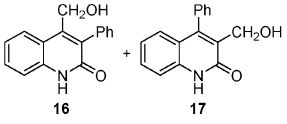
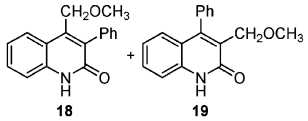
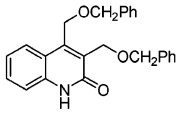
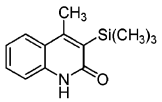
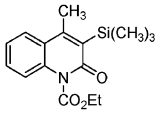
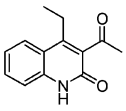
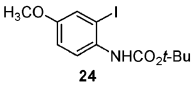
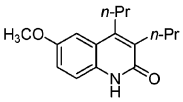
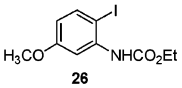
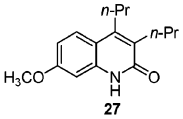
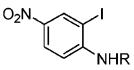
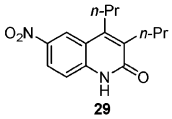
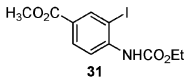
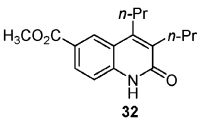
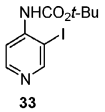
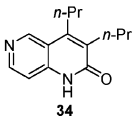
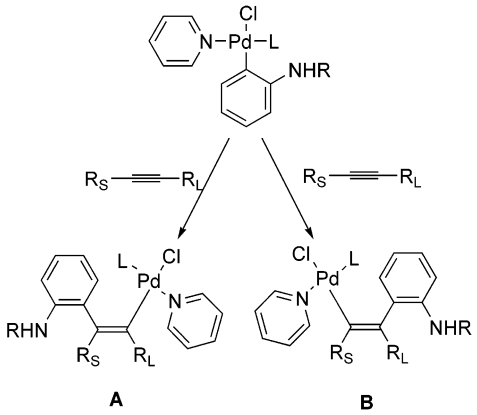
entry	*N*-substituted *o*-iodoaniline	alkyne (equiv)		product(s)	% isolated yield (ratio of isomers)
1			(5)	 **1**	71
2			(3)		69
3			(2)		58
4[b]			(5)		56
5[b]			(3)		54
6			(5)	 **5** **6**	81 (69:31)
7			(3)		82 (68:32)
8			(3)	 **7** **8**	58 (66:34)
9			(3)	 **9** **10**	56 (74:26)
10			(3)	 **11**	18
11			(3)	 **12**	14
12			(3)	 **13** **14**	66 (75:25)
13			(3)	 **15**	22
14			(5)	**15**	15
15			(5)	**15**	16
16			(3)	 **16** **17**	42 (66:34)

Table 4. (Continued)

entry	*N*-substituted *o*-iodoaniline	alkyne (equiv)	product(s)	% isolated yield (ratio of isomers)
17		$Ph{-}{\equiv}{-}CH_2OCH_3$ (3)	 **18** + **19**	60 (66:34)
18		$HOH_2C{-}{\equiv}{-}CH_2OH$ (3)	--	0
19		$BnOCH_2{-}{\equiv}{-}CH_2OBn$ (3)	 **20**	51
20		$H_3C{-}{\equiv}{-}Si(CH_3)_3$ (3)	 **21**	26
21[b]		(5)		22
22[c]		(3)	**21** +  **22**	28 (39:61)
23		$CH_3CH_2{-}{\equiv}{-}COCH_3$ (3)	 **23**	19
24	 **24**	*n*-Pr−≡−*n*-Pr (3)	 **25**	67
25	 **26**	(3)	 **27**	36
26	 R = H (**28**)	(3)	 **29**	17[d]
27	R = CO_2Et (**30**)	(3)		49
28	 **31**	(3)	 **32**	44
29[e]	 **33**	(3)	 **34**	31

[a] Standard reaction conditions: *N*-substituted *o*-iodoaniline (0.5 mmol), alkyne (1.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (5 mol %, 0.025 mmol) under 1 atm of CO in DMF (5 mL) at 100 °C for 12 h, then the crude product was treated with 1 M ethanolic NaOH (5 mL) at rt for 30 min. [b] The reaction was run at 120 °C. [c] The treatment with 1 M ethanolic NaOH was omitted. [d] 4-Nitroaniline was also isolated in a 64% yield. [e] The reaction was run for 36 h.

SCHEME 1



modes of alkyne insertion into the arylpalladium bond. However, the palladium-catalyzed annulation of the same alkynes with *o*-iodoaniline and its derivatives leading to 2,3-disubstituted indoles proceeds in most cases with excellent regioselectivity, giving only one regioisomer.[24] Since poor regioselectivity has also been observed in our synthesis of coumarins, it is reasonable to assume that the reaction conditions employed in the carbonylative annulation lead to poor discrimination between the two modes of alkyne insertion. All of our previous results on the annulation of internal alkynes suggest that the regioselectivity of the insertion is controlled almost exclusively by steric factors. The insertion of an alkyne into the arylpalladium bond results in the formation of two vinylpalladium complexes **A** and **B** (Scheme 1). Since the palladium−carbon bond is much longer than the carbon−carbon bond, the steric repulsion between the palladium atom and the larger substituent on the triple bond (R_L) in the complex **A** should be smaller than the repulsion between the same substitutent and the aryl group in the complex **B**. The major regioisomer in all annulation reactions arises from the complex **A**.

While our previous annulation reactions have been run either in the presence of triphenylphosphine or in the absence of any ligands, carbonylative annulation requires the use of pyridine, which most likely functions not only as a base, but also as a ligand. Since a Pd−N bond is much shorter than a Pd−P bond, coordination of pyridine to the palladium atom significantly increases the steric bulk of the palladium. Therefore, the difference in energy between the complexes **A** and **B** is smaller when pyridine is used, and consequently, the regioselectivity is worse.

The pyridine ligation also probably manifests itself in the fact that, like the synthesis of coumarins, this process is very sensitive to steric hindrance. Internal alkynes with very bulky substituents react sluggishly and afford the desired 2-quinolones in very low yields (entries 10 and 11). Only one regioisomer, however, is obtained in each of these reactions, further supporting the assumption that the regioselectivity is sterically controlled.

Internal alkynes bearing heterocyclic substituents, such as 1-(5-pyrimidinyl)-1-hexyne (entry 12), are also effective in the carbonylative annulation reaction giving the desired products in a 66% yield, comparable to the yields from phenylalkyl acetylenes and with slightly better regioselectivity.

We were surprised to discover that diphenylacetylene reacts very poorly under the standard reaction conditions and affords the desired 2-quinolone in only a 22% yield (entry 13). Even though diphenylacetylene is less reactive than 4-octyne, a 51% yield of the corresponding coumarin was obtained in the carbonylative annulation of diphenylacetylene by *o*-iodophenol.[6] The reactions of diphenylacetylene with other *o*-iodoaniline derivatives, such as the tosylamide (entry 14) and the trifluoroacetamide (entry 15), afforded **15** in even lower yields, even though 5 equiv of the alkyne were employed. The reason for such remarkable differences in reactivity between the aniline derivatives and the phenols is not clear.

The reactivity of internal alkynes bearing various functional groups was examined next. To our delight, the carbonylative annulation of 3-phenyl-2-propyn-1-ol (entry 16) afforded the desired 2-quinolones in a 42% yield. Even though the yield is only modest, the carbonylative annulation by *o*-iodophenol of this and other alkynes with a hydroxyl group was completely ineffective, and no coumarins were observed. Still, protection of the hydroxyl group, for example, as a methyl ether (entry 17), improves the yield of the reaction substantially. Mixtures of regioisomers were obtained in both cases with poor regioselectivity. No products were obtained in the reaction of 2-butyne-1,4-diol (entry 18), while the corresponding dibenzylated alkyne afforded the desired 2-quinolone **20** in a 51% yield (entry 19).

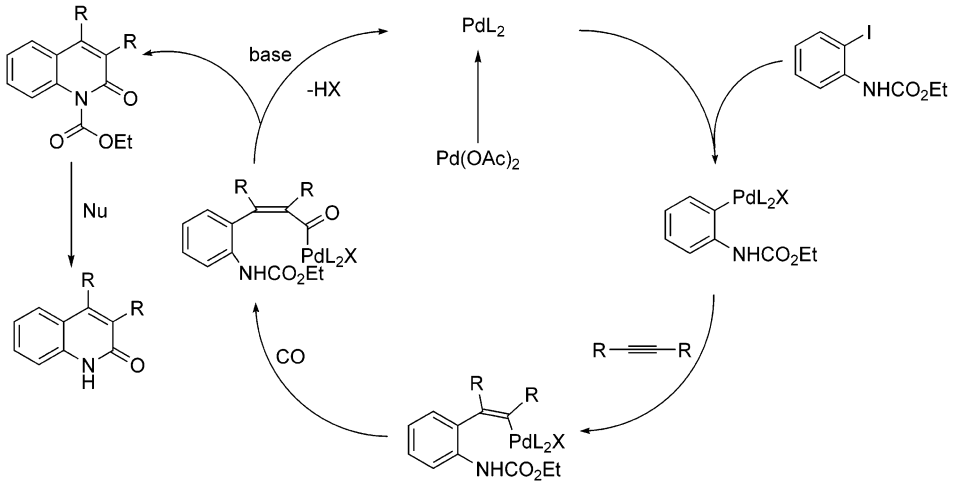
Only a 26% yield of 2-quinolone **21** was obtained when a silyl-substituted alkyne, 1-trimethylsilyl-1-propyne, was employed (entry 20). The use of a 5-fold excess of the alkyne and a higher reaction temperature (120 °C) did not improve the yield of the desired product (entry 21). We suspected that treatment of the crude product with ethanolic NaOH might be causing decomposition of the desired product. However, omission of this step resulted only in the incomplete hydrolysis of **21**, but no increase in the overall yield. The products, **21** and the still protected 2-quinolone **22**, were obtained in a 28% yield as a 39:61 mixture (entry 22).

Electron-deficient alkynes appear to be very poor substrates for the carbonylative annulation by ethyl *N*-(2-iodophenyl)carbamate. Only a 19% yield of 2-quinolone **23** was obtained in the reaction of 3-hexyn-2-one (entry 23), while the corresponding coumarin was obtained in a 61% yield.[6] Interestingly, only one regioisomer was isolated, and its structure is assumed to be analogous to the structure of the major coumarin isomer. This result is consistent with the excellent regioselectivity (90:10) observed in the carbonylative annulation of this alkyne by *o*-iodophenol. Since only a 19% yield of **23** was obtained, it is likely that the minor isomer was lost during the workup, even if it was formed in the reaction.

We have also examined the reactivity of various electron-rich and electron-poor alkyl *N*-(2-iodophenyl)-carbamates as annulating agents in the reaction with 4-octyne. Introduction of an electron-donating substituent, for example a methoxy group, *para* to the amino group (entry 24) does not affect the yield of the carbonylative annulation. The corresponding 2-quinolone **25** was obtained in a 67% yield, comparable to the yield of the parent system (entry 2). However, only a 36% yield

(24) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

SCHEME 2

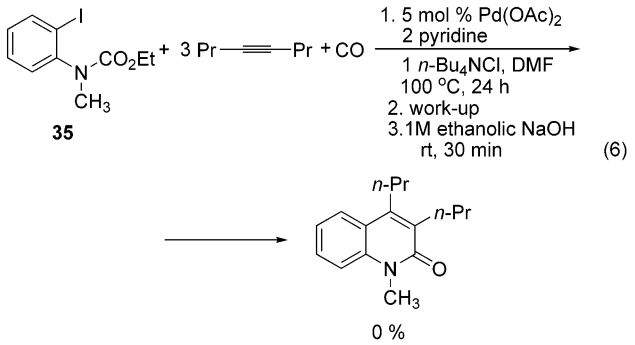


of the desired product was obtained from the *o*-iodoaniline derivative with a methoxy group *para* to the iodine (entry 25). Still, this result is an improvement over the reaction of the analogous 2-iodo-5-methoxyphenol, which was completely unreactive in the carbonylative annulation of 4-octyne, undergoing instead rapid deiodination to produce 3-methoxyphenol in an 82% yield.[6] It appears that the presence of two strong electron-donating groups in positions *ortho* and *para* to the iodine atom reduces the stability of the aryl iodide, with deiodination occurring much faster than oxidative addition to the palladium complex. The presence of the carbamate protecting group reduces the electron-donating ability of the amino substituent, thus increasing the stability of the aryl iodide and allowing it to participate in carbonylative annulation process.

A different picture emerged from the reactions of electron-poor iodoanilines. Unlike the reactions of the parent 2-iodoaniline, the reaction of unprotected 2-iodo-4-nitroaniline afforded the desired 2-quinolone **29**, albeit only in 17% yield (entry 26). This reaction was very clean, and the only other product of the reaction was the deiodinated 4-nitroaniline, isolated in a 64% yield. The formation of 2-quinolone **29** in this reaction further supports the idea that the poor reactivity of the parent 2-iodoaniline relates to the high nucleophilicity of the amino group. Even though unprotected 2-iodo-4-nitroaniline afforded some of the desired 2-quinolone, protection of the amino group as an ethyl carbamate is still necessary to obtain a satisfactory yield of **29** (49%, entry 27). The corresponding 4-methoxycarbonyl derivative **31** also afforded the 2-quinolone **32** in a similar 44% yield (entry 28). Thus, the presence of electron-withdrawing substituents on the aromatic ring of the 2-iodoanilines lowers the yield of the carbonylative annulation. A possible reason for this is the decreased stability of the carbamates toward hydrolysis, since the presence of an electron-withdrawing group should increase the positive charge on the carbonyl carbon.

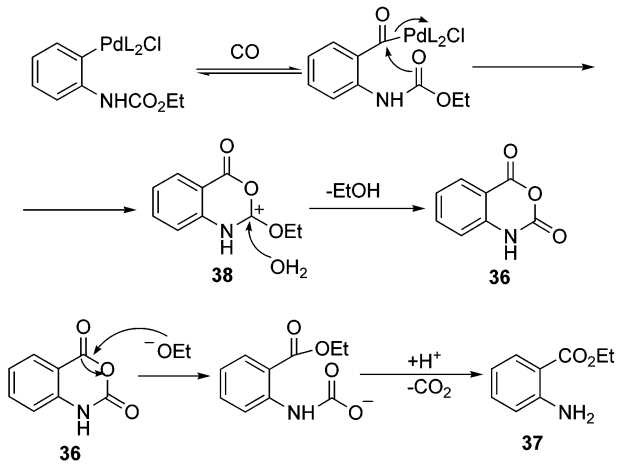
Another electron-poor aniline, a carbamate derivative of 4-amino-3-iodopyridine **33**, also afforded a low 31% yield of the corresponding 6-aza-2-quinolone **34** (entry 27). Moreover, this reaction was very slow and only reached completion in 36 h.

Mechanism. The mechanism of this process is undoubtedly analogous to the mechanism proposed for the synthesis of coumarins.[6] It is shown in Scheme 2 and involves (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst; (2) oxidative addition of the *N*-substituted *o*-iodoaniline to Pd(0), generating an arylpalladium complex; (3) insertion of the alkyne triple bond into the arylpalladium bond to give a vinylpalladium complex; (4) insertion of CO to generate an acylpalladium complex; and (5) nucleophilic attack of the nitrogen on the carbonyl group of the acylpalladium complex leading to formation of the 2-quinolone and regeneration of Pd(0). Removal of the protecting group from the nitrogen occurs after formation of the amide bond, at least in the case of the carbamate derivatives. It is not clear whether deprotonation of the amino group is necessary for the nucleophilic attack to occur. It is likely that deprotonation occurs in the case of the tosyl- and trifluoroacetamide derivatives, but the situation with the carbamate derivatives is not obvious. On one hand, the carbamate is significantly less acidic than the tosylamide or trifluoroacetamide. On the other hand, the reaction with the carbamate **35**, lacking the amide hydrogen, (eq 6) did not produce any of the annulation product.



Just as in the carbonylative annulation of internal alkynes with *o*-iodophenols,[6] in this process we have never observed any 4-quinolones, which arise from the reverse order of alkyne/CO insertion into the carbon−palladium bond. Previously, we have established that even though the insertion of CO into the arylpalladium bond to form an acylpalladium complex occurs under our

SCHEME 3



reaction conditions, the reaction of this acylpalladium complex with an internal alkyne is apparently very slow.[6b] Therefore, in the absence of any internal nucleophile capable of trapping the acylpalladium complex, the acylpalladium complex undergoes decarbonylation to the original arylpalladium complex, which eventually reacts with the internal alkyne, and is thus converted into the coumarin or the 2-quinolone. Further evidence supporting this scheme has been obtained during our investigation of the carbonylative annulation of *N*-substituted *o*-iodoanilines.

In most of the reactions employing ethyl *N*-(2-iodophenyl)carbamate a minor byproduct can be isolated, along with the desired 2-quinolone. The byproduct is either isatoic anhydride (**36**) (in the reactions without ethanolic NaOH treatment) or ethyl 2-aminobenzoate (**37**) (in the reactions with a basic workup). In the reaction with 4-octyne the yield of the byproduct is around 10−12%. However, in the reactions employing a very unreactive alkyne, such as 4,4-dimethyl-2-pentyne or 1-phenyl-3,3-dimethyl-1-butyne (Table 4, entries 10 and 11), ethyl 2-aminobenzoate was isolated in 30 and 39% yields, respectively. In almost all reactions this byproduct was detected in the crude product mixtures by ^{1}H NMR spectroscopy, but it was not isolated in a pure form and the exact yield was not determined. The mechanism of formation of these byproducts is shown in Scheme 3. Insertion of CO into the arylpalladium bond, followed by intramolecular attack by the oxygen atom of the carbamate group on the carbonyl of the acylpalladium complex, leads to the intermediate **38**. Attack on the oxonium ion **38** by a water molecule and elimination of ethanol lead to the formation of isatoic anhydride. Upon treatment with ethanolic NaOH, the more electrophilic ester carbonyl group is attacked by an ethoxide anion generating a carbamic acid anion, which spontaneously loses CO_2 giving rise to ethyl 2-aminobenzoate. A similar intramolecular attack of an amide oxygen on an acylpalladium complex has been previously observed.[25]

These data support the mechanistic scheme outlined above. An acylpalladium complex is generated under our reaction conditions, but it is not very reactive. The ratio of the products from initial CO insertion and initial alkyne insertion depends on the rates of the intramolecular trapping of the acylpalladium complex and the irreversible insertion of the alkyne into the arylpalladium bond. In most cases, insertion of the alkyne is a much faster process, and only in the reactions with very unreactive alkynes (Table 4, entries 10 and 11) does the intramolecular attack of the carbamate oxygen predominate.

(25) Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **1996**, 997.

Conclusions

We have successfully extended the palladium-catalyzed carbonylative annulation of internal alkynes to reactions with *o*-iodoaniline derivatives, thus providing a new synthesis of 3,4-disubstituted 2-quinolones. A crucial aspect of the synthesis is the choice of the protecting group on the nitrogen atom of the iodoaniline. The most effective groups are alkoxycarbonyl, *p*-toluenesulfonyl, and trifluoroacetyl. A wide variety of internal alkynes bearing alkyl, aryl, heteroaryl, hydroxyl, and alkoxyl substituents has been employed in this process affording the desired 2-quinolones in 50 to 80% yields. Though the use of unsymmetrical alkynes leads to the formation of mixtures of regioisomers with low regioselectivity, these products are easily separable by column chromatography. Electron-rich iodoanilines with substituents para to the amino group are also effective in the carbonylative annulation. The carbonylative annulation of electron-poor iodoaniline derivatives affords 2-quinolones in lower yields than the parent system.

Experimental Section

General Procedure for the Palladium-Catalyzed Synthesis of 3,4-Disubstituted 2-Quinolones. Ethyl *N*-(2-iodophenyl)carbamate (0.5 mmol), the alkyne (1.5 mmol), pyridine (1.0 mmol), *n*-Bu_4NCl (0.5 mmol), and $Pd(OAc)_2$ (5 mol %, 0.025 mmol) were placed in a 4 dram vial and then dissolved in 5 mL of DMF. The vial was purged with CO for 2 min and then connected to a balloon of CO. The reaction mixture was stirred at 100 °C for 12 h, allowed to cool to room temperature, diluted with EtOAc, washed with water, and concentrated under reduced pressure. The residue was treated with 5 mL of 1 M ethanolic NaOH at room temperature for 30 min. Then satd aq NH_4Cl (15 mL) was added, and the resulting mixture was extracted with EtOAc. The organic extracts were combined, washed with satd aq NH_4Cl, and water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was separated by column chromatography on silica gel.

3,4-Dipropyl-2(1*H*)-quinolinone (1): white solid; mp 159−160 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 1H), 7.43 (ddd, J = 1.2, 6.8, 8.0 Hz, 1H), 7.38 (dd, J = 1.2, 8.0 Hz, 1H), 7.20 (ddd, J = 1.4, 6.8, 8.2 Hz, 1H), 2.86−2.90 (m, 2H), 2.74−2.78 (m, 2H), 1.59−1.71 (m, 4H), 1.05−1.12 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 164.3, 147.6, 137.5, 131.4, 129.2, 124.5, 122.3, 120.4, 116.5, 31.1, 29.3, 23.6, 22.9, 14.8, 14.7; IR (neat, cm^{-1}) 2963, 2868, 1661; MS *m*/*z* (rel intensity) 229 (67, M^+), 228 (52), 214 (100), 200 (47), 186 (41); HRMS calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1470.

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Supporting Information Available: Procedures for the preparation of starting materials; characterization data and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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