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Combining Isocyanides with Carbon dioxide in Palladium-Catalyzed Heterocycle Synthesis: N3-Substituted Quinazoline-2,4(1H,3H)-diones via a Three-Component Reaction.

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ABSTRACT: We report a Pd-catalyzed three-component reaction of 2-bromoanilines, carbon dioxide and isocyanides. The combination of these two readily available C₁-reactants, featuring a huge difference in kinetic and thermodynamic stability, is hitherto unprecedented in transition metal catalysis. With this one-pot three-component reaction N3-substituted quinazoline-2,4(1H,3H)-diones are obtained in moderate to high yields in a completely regio- and chemoselective manner. Our approach easily allows variation of the arene and N3-substitution pattern of the desired heterocycle. The formal synthesis of different APIs illustrates its practical applicability. In addition, the methodology also allows for a convenient and selective ¹³C-labelling through the use of ¹³CO₂. This is illustrated for [2-¹³C]-2,4-dichloro-6,7-dimethoxyquinazoline synthesis, a key intermediate for several APIs.

INTRODUCTION

The use of abundant, non-toxic and renewable CO₂ in organic synthesis is of actual interest and continues to attract attention of the scientific community.¹ Despite the significant advancements made in this area, especially by transition metal-catalyzed reactions, the incorporation of carbon dioxide into heterocycles such as benzo-annulated heteroarenes has been less explored.² Other readily available C₁-building blocks, like isocyanides (RNC)³ and CO,⁴ have been well explored for this purpose. Obviously, the thermodynamic stability and chemical inertness of CO₂ is one reason for this striking difference. The combination of CO₂ and RNC in a multicomponent reaction would be an attractive additional way to efficiently synthesize heterocycles, as in such an approach a carbonyl and imine moiety can be introduced simultaneously. However, the combination of both in transition-metal catalyzed reactions is still unprecedented.⁵ This is presumably due to the difference in kinetic and thermodynamic stability of both C₁-reactants. Moreover, CO₂ is a gas with a limited solubility in organic solvents, which decreases with increasing temperature, while RNC are liquids or solids which fully solubilize, further reinforcing the challenge to combine both reactants in a multicomponent synthesis. For our method development studies, we selected the coupling of 2-haloanilines (**1**) with isocyanides (**2**) and carbon dioxide as a suitable model system (Scheme 1). While the reaction of 2-haloanilines with RNC via double insertion is known to construct 3-iminoindol-2-amines (**6**, Scheme 1, route A),^{7a} the three-component coupling with CO₂ to construct benzo-annulated heterocycles has not yet been reported.^{6,7} Even when an effective catalytic system which sufficiently activates CO₂ and tunes the RNC insertion reactivity can be identified still two reaction products can be obtained, namely 2-amino-4H-benzo[d][1,3]oxazin-4-one (**5**)⁸ and 4-imino-1,4-dihydro-2H-benzo[d][1,3]oxazin-2-one (**4**) (Scheme 1, route B and C). Therefore, both regio- and chemoselectivity in the reaction of **1** with the two C₁-reactants has to be controlled. As no examples of heterocycles of type **4**

Scheme 1. Possible reaction products.

Scheme 2. Examples of biologically active *N*3-substituted quinazolin-4(3*H*)-ones and *N*1,*N*3-disubstituted quinazoline-2,4(1*H*,3*H*)-diones.

could be found in the literature,⁹ a spontaneous rearrangement into *N*3-substituted quinazoline-2,4(1*H*,3*H*)-diones **3** via deprotonation by base was anticipated. This is interesting as heterocycles **3** are an important class of compounds, which are key intermediates for the synthesis of biologically active *N*3-substituted quinazolin-4(3*H*)-ones and *N*1,*N*3-disubstituted quinazoline-2,4(1*H*,3*H*)-diones (Scheme 2).¹⁰ Classical synthesis of *N*3-substituted quinazoline-2,4(1*H*,3*H*)-diones^{11,12} are typically based on more toxic reactants [e.g. CO, phosgene, phosgene derivatives (isocyanates, chloroformates, Boc_2O), azides]¹³ and often involve substrates, requiring multistep synthesis resulting in a low overall efficiency and a difficult variation of the substitution pattern of the arene ring. Moreover, *N*-alkylation of quinazoline-2,4(1*H*,3*H*)-diones results in a mixture of *N*-mono- and dialkylated reaction products.¹⁴ Only by transformation into the corresponding 2,4-bis(trimethylsilyloxy)quinazoline selective *N*-alkylation can be achieved.^{14b, 15} However, this occurs at the *N*1 rather than the *N*3-position. In view of the above, the envisioned synthesis of **3** via a three-component reaction of two C_1 -reactants (CO_2 , RNC), featuring a low

toxicity,¹⁶ and readily available 2-haloanilines **1** is interesting from both a fundamental and synthetic point of view.

RESULTS AND DISCUSSION

Initially, the synthesis of 3-*tert*-butylquinazoline-2,4(1*H*,3*H*)dione (**3a**) from *o*-bromoaniline (**1a**), *t*BuNC (**2a**) and CO₂ was investigated in the presence of several palladium phosphine complexes (Table 1). In toluene BuPAD₂ proved to be a suitable ligand for Pd(OAc)₂

Table 1. Model Reaction and Selected Optimization Data^a

Entry	Ligand	Base	T (°C)	Solvent	CO ₂ (bar)	Time (h)	Yield 3a (%) ^b
1	BuPAD ₂	Cs ₂ CO ₃	80	Toluene	10	4	37 ^c
2	Xphos	Cs ₂ CO ₃	80	Toluene	10	4	44
3	Dppe	Cs ₂ CO ₃	80	Toluene	10	4	0
4	/	Cs ₂ CO ₃	80	Toluene	10	4	0 ^d
5	BuPAD ₂	K ₂ CO ₃	80	Toluene	10	4	0
6	BuPAD ₂	K ₃ PO ₄	80	Toluene	10	4	0
7	BuPAD ₂	NEt ₃	80	Toluene	10	4	0
8	BuPAD ₂	Cs ₂ CO ₃	60	Toluene	10	4	9 ^e
9	BuPAD ₂	Cs ₂ CO ₃	100	Toluene	10	4	5 ^f
10	BuPAD ₂	Cs ₂ CO ₃	80	THF	10	4	65
11	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	10	4	79
12	BuPAD ₂	Cs ₂ CO ₃	80	CH ₃ CN	10	4	8
13	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	20	4	75
14	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	5	4	61
15	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	1	4	42
16	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	10	7	48
17	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	10	7	91 (94) ^g
18	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	0	7	0 ^h
19	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	10	7	57 ^{i,j}
20	BuPAD ₂	Cs ₂ CO ₃	80	1,4-dioxane	1	24	60 ^{i,k}
21	BuPAD ₂	DBU	80	1,4-dioxane	1	20	65 ^{g,l}

^a Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (1.2 equiv), Pd(OAc)₂ (10 mol %), ligand (20 mol %), Cs₂CO₃ (2.0 equiv), solvent (1.0 mL), CO₂ (x bar), 80 °C, time. BuPAD₂ = diadamantyl-*n*-butylphosphine, XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, Dppe = 1,2-bis(diphenylphosphino)ethane. ^b ¹H NMR yield using 1,3,5-trimethoxybenzene as internal standard. Number in parenthesis is isolated yield. ^c 55% conversion **1a**. ^d Pd(OAc)₂ and ligand were omitted. ^e 40% conversion **1a**. ^f 99% conversion **1a**. 60% of undesired **6a** was obtained. ^g Pd(OAc)₂ (3 mol %), BuPAD₂ (6 mol %) were used. ^h Ar atmosphere (10 bar). 65% of undesired **6a** was formed. ⁱ Pd(OAc)₂ (1 mol %), BuPAD₂ (2 mol %) were used. ^j 80% conversion **1a**. ^k 89% conversion of **1a**. ^l 92% conversion of **1a**.

(10 mol %) affording **3a** in moderate yields (entries 1-3). As expected, without catalyst no **3a** was obtained (entry 4). The use of Cs₂CO₃ was crucial as other bases (e.g. K₂CO₃ and NEt₃) or no base did not yield the desired heterocycle **3a** (entries 5-7). Besides the base, also the reaction temperature turned out to be important. Interestingly, at 100 °C *N*-*tert*-butyl-3-(*tert*-butylimino)-3*H*-indol-2-amine (**6a**) was the major compound (60%), while at 80 °C only **3a** was selectively formed (entries 1, 9). However, at 60 °C only a low conversion of **1a** and yield of **3a** was observed (entry 8). Solvent screening revealed that 1,4-dioxane is the optimal solvent for this transformation (entries 1, 10-12). A lower yield of **3a** was obtained when the reaction time was prolonged from 4 to 7 hours (entries 11, 16). On the other hand, additional reduction of the Pd(OAc)₂ and BuPAD₂ loading to 3 and 6 mol %, respectively, delivered the desired **3a** in 94% isolated yield in 7 hours (entry 17). Further reduction of catalyst loading gave incomplete reaction (entry 19). Interestingly, **3a** could also be obtained at 1 bar of CO₂, but a slower conversion of **1a** was then observed (entry 20). This experiment shows that the chemoselectivity obtained is not pressure related. When Ar was used as reaction atmosphere instead of CO₂, **6a** was obtained as the only product in 65% (entry 18). The full details of the optimization process can be found in the SI.

Table 2. 2-Bromoaniline (**1**) scope.^a

Entry		Yield (%)	Entry		Yield (%)
1		3a 94 ^b 92 ^d	9		3i 85 ^b
2		3b 89 ^b	10		3j 78 ^c
3		3c 88 ^b	11		3k 49 ^b
4		3d 84 ^b	12		3l 83 ^b
5		3e 51 ^c	13		3m 96 ^b
6		3f 85 ^b	14		3n 55 ^b
7		3g 50 ^c 66 ^e	15		3o 73 ^c
8		3h 73 ^b	16		3p 77 ^c

^a Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2a** (1.2 equiv), Pd(OAc)₂ (3 mol %), BuPAD₂ (6 mol %), Cs₂CO₃ (2.0 equiv), 1,4-dioxane (1.0 mL), CO₂ (10 bar), 80 °C. Isolated yield. ^b 7 h. ^c 16 h. ^d 5 mmol scale. ^e Pd(OAc)₂ (10 mol %), BuPAD₂ (20 mol %), CO₂ (2 bar), N₂ (1 bar), 16 h.

With the optimized reaction conditions in hand [**1a** (1.0 equiv), **2a** (1.2 equiv), Pd(OAc)₂ (3 mol %), BuPAD₂ (6 mol %), Cs₂CO₃ (2.0 equiv), 1,4-dioxane (1.0 mL), CO₂ (10 bar), 80 °C], we evaluated the scope of the reaction (Table 2). First, **2a** was coupled with a variety of 2-bromoanilines (**1**). Substrates bearing electron-donating (**1a-h**) substituents were well tolerated, irrespective of the position, and the corresponding 3-*tert*-butylquinazoline-2,4-(1*H*,3*H*)-diones (**3a-h**) were obtained in moderate to high yield. Even very electron-rich 2-bromoanilines such as **1g** could be employed. Similarly, moderate, such as halogens (**1i-m**), and strong electron-withdrawing substituents, as exemplified by a trifluoromethyl (**1o-p**) and an acyl moiety (**1n**), gave the corresponding 3-*tert*-butylquinazoline-2,4-(1*H*,3*H*)diones (**3i-p**) in a good yield. Notably, the reaction of **1a** and **2a** with CO₂ could readily be performed on 5 mmol scale.

Next, the scope of the reaction with respect to the RNC reagent (**2**) was investigated with **1a** as the coupling partner (Table 3). Besides *t*BuNC (**2a**), other tertiary isocyanides (**2b-c**) were well tolerated, even the very bulky 1-adamantyl isocyanide (**2b**). Reactions of isocyanides involving transition-metal catalysis are often limited to tertiary RNC as primary and secondary RNC have a more electrophilic isocyanide C- atom, which increases their reactivity for insertion.^{3, 17} Therefore, we were pleased to observe that this novel three-component reaction could be extended towards secondary (**2d-f**) and even primary RNC (**2g-i**) yielding the target compounds **7d-i** selectively in moderate to high yield, without the formation of **6**. The structures of all 3-substituted quinazoline-2,4-(1*H*,3*H*)diones (**3,7**) were confirmed by ¹H NMR, ¹³C NMR and HRMS. Moreover, structures of **7b** and **7c** were unambiguously established by single-crystal X-ray measurements (see Figure 1 and SI).

Table 3. Isocyanide (**2**) scope.^a

Entry		Yield (%)	Entry		Yield (%)
1		7b 85	5		7f 56
2		7c 71	6		7g 91
3		7d 65	7		7h 58
4		7e 70	8		7i 67

^a Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2** (1.2 equiv), Pd(OAc)₂ (3 mol %), BuPAD₂ (6 mol %), Cs₂CO₃ (2.0 equiv), 1,4-dioxane (1.0 mL), CO₂ (10 bar), 80 °C, 16 h. Isolated yield.

Figure 1. Molecular structure of **7c** in the crystal. Only one molecule of the asymmetric unit is depicted. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms (except H₁) are omitted for clarity.

Many important active ingredients (AI) containing the quinazoline-2,4(1*H*,3*H*)-dione scaffold have unsymmetrical substitution patterns across the two nitrogen atoms (Scheme 2), which generally cannot be obtained selectively by a direct alkylation reaction with RX on the parent *N*-unsubstituted quinazolinedione core (*vide supra*). For such cases, our three-component reaction provides an efficient solution as it directly delivers *N*3-substituted quinazoline-2,4(1*H*,3*H*)-diones. A subsequent alkylation at *N*1 can be easily performed under standard alkylation conditions, as exemplified for the synthesis of **8** from **3a** (Scheme 3) and for alkaloid **10**¹⁸ from **7i** (Scheme 4). Considering that easily accessible **2a** is a convertible RNC, the ^tBu moiety in the *N*3-position of the reaction product can also serve as a protecting group allowing initial selective *N*1-functionalization, followed by *N*3-^tBu cleavage with HCl yielding *N*1-substituted quinazoline-2,4(1*H*,3*H*)-diones. This is exemplified for the transformation of **3a** into **9** (Scheme 3).

Scheme 3. Synthesis of **9** via *N*1-benylation of **3a** and *N*3-^tBu cleavage of **8**.

Scheme 4. Synthesis of alkaloid **10** via methylation of **7i**.

Selective preparation of isotopically labelled APIs is an important part for modern drug discovery processes (e.g. for metabolic studies, internal standards). Readily available, stable and safe C₁ isotopically labelled reactants are ideal for this purpose. In the past decade ¹³COgen and Sila¹³COgen, both synthesized from ¹³CO₂, have been developed by Skrydstrup and co-workers as safe ¹³CO sources for labelling through carbonylation.¹⁹ As ¹³CO₂ is a non-toxic, non-flammable and cheap carbonylating reactant (Scheme 5), direct use without pre-transformation into ¹³CO releasing reactants is interesting, whenever

Scheme 5. ^{13}C -carbonylating reactants.²²

Scheme 6. Classical and three-component approach for 2,4-dichloro-6,7-dimethoxyquinazoline (**11**) synthesis.

possible, and we therefore examined its potential in our three-component protocol.²⁰ 2,4-Dichloro-6,7-dimethoxyquinazoline (**11**) was selected for this purpose as it is an important precursor for well-known APIs like Prazosin, Afluzosin and Doxazosin (Scheme 6).²¹ To obtain [2- ^{13}C]-3-*tert*-butyl-5,6-dimethoxyquinazoline-2,4(1*H*,3*H*)dione ([2- ^{13}C]-**3g**) a minimum amount of $^{13}\text{CO}_2$ preferentially needs to be used. Moreover, challenging substrate **1g** is one of the least reactive under the standard conditions of our protocol (Table 2, entry 7). Based on these considerations, a higher catalyst loading and lower pressure was selected for labelling. Flushing of the reactor was done with N₂ rather than $^{13}\text{CO}_2$ to avoid spilling. Then, 2 bar of $^{13}\text{CO}_2$ were introduced which gave 72% of [2- ^{13}C]-**3g** after 16 hours with 10% catalyst loading. Two bar $^{13}\text{CO}_2$ corresponds to only 4 equivalents and represents just 13% of the price of all the components used in this reaction.²² Reaction of [2- ^{13}C]-**3g** with POCl₃ finally yields [2- ^{13}C]-2,4-dichloro-6,7-dimethoxyquinazoline ([2- ^{13}C]-**11**) in 86% yield. Interestingly, the classical routes reported for **11** also start from veratrole and require more steps than our approach (Scheme 6).^{21,24-25} Moreover, ^{13}C carbonylating agent NH₂ ^{13}C ONH₂ (route A) is much more expensive and NaO ^{13}C N (route B) is not commercially available.

A plausible mechanism for the formation of **3** from **1** is presented in Scheme 7. Oxidative addition of 2-bromoanilines(**1**) to Pd⁰L yields complex **A**. R²NC (**2**) insertion into Ar-Pd^{II} gives

Scheme 7. Proposed mechanism for the synthesis of 3-substituted quinazoline-2,4(1*H*,3*H*)diones (**3**) from 2-bromoanilines (**1**), R^2NC (**2**) and CO_2 .

B.²³ This complex is in equilibrium with dimer **B**₂. A similar dimerization might take place in case of complex **A** (not shown). Subsequent reaction with CO_2 forms palladacycle **D**. Reductive elimination delivers **4**, which spontaneously rearranges into reaction product **3** under the basic reaction conditions, and regenerates the active Pd^0L complex. Notably, chemoselectivity is determined in complex **B** where a second isocyanide insertion is in competition with reaction with CO_2 . Under Ar atmosphere only **C** can be formed finally yielding **6**. However, in the presence of CO_2 , the Lewis acidic Pd^{II} centre in complex **B** activates CO_2 for nucleophilic attack by nitrogen favouring formation of **D** and finally yielding *N*3-substituted quinazoline-2,4(1*H*,3*H*)-dione **3**.

Several control experiments were performed to support the proposed reaction mechanism. Rearrangement of **4** is supported by calculations which confirmed that **3** is thermodynamic more stable (see SI). In addition, we performed an experiment starting from *N*-benzyl-2-bromoaniline (**1q**) and *tert*-butyl isocyanide (**2a**) under the standard conditions (Scheme 8, A). In this case, 1-benzyl-4-*tert*-butylimino-1,4-dihydro-2*H*-benzo[*d*][1,3]oxazin-2-one (**4q**) should be formed *in situ*, which cannot rearrange by deprotonation. However, this type of compounds is known to be unstable and susceptible for hydrolysis.⁹ In accordance with this we obtained 68% of *N*-*tert*-butyl-*N'*-benzyl-2-aminobenzamide (**12**). This product is however not formed by a simple direct reaction of aryl bromide **1q**, **2a** and water. Carbon dioxide is essential for this transmutation, as supported by a similar experiment under Ar atmosphere yielding only *N*-benzylisatin (**13**) in 84% (Scheme 8, B). **13** is obtained by hydrolysis of the initially formed di-(*tert*-butylimino)isatin. Water in both experiments comes from Cs_2CO_3 base. When we dried commercial Cs_2CO_3 and worked in dry dioxane a reduced amount of **12** was observed under CO_2 pressure in accordance with the presence of a lower amount of water (Scheme 8, C). However, still no **4q** could be isolated but instead 45% substrate **1q** remained. Clearly, water also influences the formation of intermediate **4**. The reactions are very sensitive to the *N*-substituent of the aniline as further exemplified using methyl (2-bromophenyl)carbamate (**1r**) under Argon atmosphere. *N*-*tert*-butyl-*N'*-(methoxycarbonyl)-2-aminobenzamide (**14**) was obtained in this case and no isatin (Scheme 8, D), while *N*-benzyl-2-bromoaniline (**1q**) only gave benzamide when working under CO_2 atmosphere

Scheme 8. Control experiments with *N*-benzyl-2-bromoaniline (**1q**) and methyl (2-bromophenyl)carbamate (**1r**). Bn = benzyl.

(Scheme 8, A and B). By performing an experiment with $^{13}\text{CO}_2$ it could be proven that C2 comes from CO_2 , and not from hydrolysis of an imine built in via an isocyanide reactant (see Scheme 6 and SI). ^{31}P NMR on model complexes and the crude reaction mixture point to **B₂** as the resting state of the catalyst (see SI).

Concerning the order of the events in the catalytic cycle there are two possible pathways, the one presented in Scheme 7 where oxidative addition is occurring first followed by R^2NC insertion and subsequent reaction with CO_2 , or one which starts with the formation of the cesium carbamate salt of 2-bromoaniline (**1a**), CO_2 and Cs_2CO_3 . To find out whether the latter is a viable reaction pathway, we performed some model experiments to evaluate the stability of the 2-bromophenylcarbamate salt (**16**). As it is easier to work with a fully soluble organic base we decided to execute these experiments with DBU, which was found to also be a suitable base for our reaction protocol (Table 1, entry 21). When 2-bromoaniline (**1a**) and 1 equiv DBU were mixed in dioxane in the presence of 1 atmosphere CO_2 and stirred for 30 minutes at rt, no DBU salt of 2-bromophenylcarbamic acid (**16**) was formed (Scheme 9, A). Only **1a** was fully recovered and 70% of the $[\text{DBUH}^+][\text{HCO}_3^-]$ salt (**15**) was isolated.²⁶ Even when applying 40 bar of CO_2 at 40 $^\circ\text{C}$ for 16 h a similar result was obtained (Scheme 9, B). Therefore, we decided to also start from a stable methyl carbamate precursor which upon hydrolysis could give access to **16**. When methyl (2-bromophenyl)carbamate (**1r**), 1 equiv DBU and 1 equiv water were brought in dioxane and heated at 80 $^\circ\text{C}$, 38% recovered carbamate **1r**, 61% 2-bromoaniline (**1a**) and 53% $[\text{DBUH}^+][\text{HCO}_3^-]$ salt (**15**) were obtained

Scheme 9. Control experiments to check the stability of the DBU salt of 2-bromophenylcarbamic acid (**16**).

(Scheme 9, C). These experiments point to a very unstable 2-bromophenylcarbamate salt (**16**) and therefore it is unlikely to be involved in our catalytic cycle.²⁷

CONCLUSIONS

In conclusion, we developed a novel three-component reaction between readily available 2-bromoanilines, RNC and CO_2 affording *N*3-substituted quinazoline-2,4-(1*H*,3*H*)-diones in a single step. Our approach easily allows variation of the arene moiety and the *N*3-position avoiding the use of more toxic reactants typically involved in the classical routes. Besides tertiary RNC the reaction also tolerates secondary and primary RNC, which are often problematic in transition-metal catalyzed reactions. The obtained *N*3-substituted quinazoline-2,4-(1*H*,3*H*)-diones were easily post-functionalized, illustrating the synthetic potential of our methodology. Also selective labelling can be conveniently performed when using cheap $^{13}\text{CO}_2$. The synthetic method disclosed provides the first example in which a kinetic and thermodynamic unreactive (CO_2) and reactive (RNC) C1-reactant are successfully combined in a transition metal-catalyzed three-component reaction. Even at 1 atm of CO_2 complete regio- and chemoselectivity is observed.

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