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Tandem Palladium-Catalyzed Urea Arylation–Intramolecular Ester Amidation: Regioselective Synthesis of 3-Alkylated 2,4-Quinazolinediones

Michael C. Willis,* Robert H. Snell, Anthony J. Fletcher, and Robert L. Woodward

Department of Chemistry, University of Bath, Bath, BA2 7AY, United Kingdom

m.c.willis@bath.ac.uk

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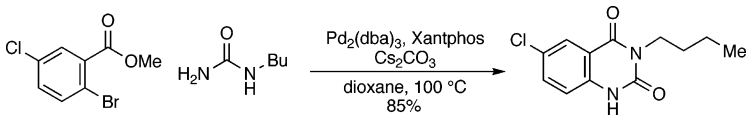
ABSTRACT



***o*-Halo benzoates can be combined with monoalkyl ureas in a tandem palladium-catalyzed arylation–ester amidation sequence to deliver quinazolinedione products. The reactions are regioselective for formation of the 3-*N*-alkyl isomers. Significant variation of both coupling partners is possible, allowing the synthesis of a diverse array of substituted quinazolinediones, exemplified by the preparation of a simple unsymmetric-dialkylated natural product.**

The quinazolinedione motif is an important heterocycle, as not only are these units embedded in a variety of natural products and designed molecules, but they also serve as precursors to a range of related structures.[1] Quinazolinediones are responsible for a variety of biological responses, including applications to hypertension,[2] diabetes,[3] and immunosuppression.[4] A large number of these biologically interesting examples feature unsymmetrical alkylation patterns across the two *N*-atoms; the natural product **1**,[5] and medicinal agents **2**[6] and **3**[3] are illustrative examples (Figure 1). A significant complication in the synthesis of these molecules is that alkylation of the parent heterocycle often results in the formation of mixtures of regioisomers,[7] and this has led to the development of synthetic routes involving the stepwise introduction and functionalization of the individual *N*-atoms.[8] In this Letter we report a new quinazolinedione synthesis that involves the regioselective introduction of both *N*-atoms in a single operation.

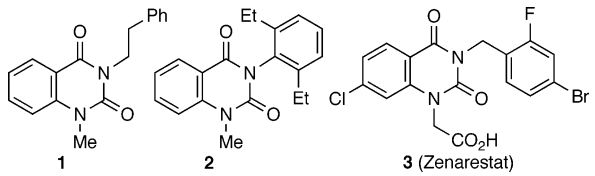


Figure 1. Representative alkylated quinazolinediones.

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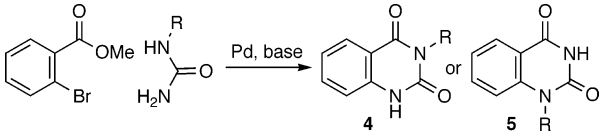
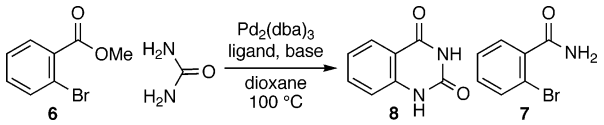
Continuing our interest in the application of palladium-catalyzed C−N and C−O bond forming reactions in tandem processes for heterocycle synthesis,[9] we speculated that the combination of an *N*-alkyl urea with an *o*-halo benzoate would provide a direct route to monoalkylated quinazolinediones (Scheme 1).[10,11] The heterocycle would be constructed by using a tandem reaction sequence involving Pd-catalyzed urea arylation and base-promoted ester amidation. The utility of the process would be dependent on achieving selectivity for either the 3-*N*-alkyl (**4**) or 1-*N*-alkyl (**5**) regioisomer. We anticipated that regiocontrol would be possible by dictating the order of the two bond-forming steps, and by the regioselectivity of the arylation reaction.

Scheme 1. Tandem Urea Arylation−Ester Amidation Route to Quinazolinediones



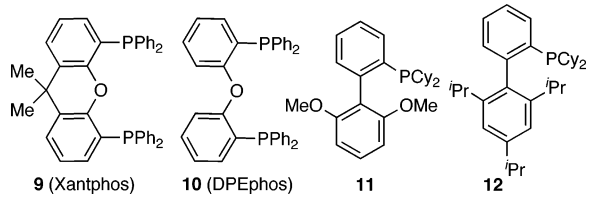
Although palladium-catalyzed *N*-arylation is now a routine operation in synthetic chemistry,[12] there are only a handful of reports of the use of urea nucleophiles.[13,14] To establish that the proposed route was feasible we chose to ignore the issue of regioselectivity and to focus on the coupling of *o*-bromo benzoate **6** and urea (Table 1). On the basis of literature precedent we selected Xantphos[15] as the initial ligand for study;[13] reaction between benzoate **6** and urea employing NaO^{t}Bu as base delivered only amide **7** in 21% yield (entry 1). However, the use of the weaker base Cs_2CO_3 provided the parent quinazolinedione **8** in 43% yield (entry 2). Simply extending the reaction time to 48 h increased the yield of **8** to 89% (entry 3). In an effort to reduce the reaction time we briefly explored the use of the

Table 1. Reaction Optimization[a]



entry	ligand	base	time (h)	product	yield[b] (%)
1	**9**	NaO^{t}Bu	24	**7**	21
2	**9**	Cs_2CO_3	24	**8**	43
3	**9**	Cs_2CO_3	48	**8**	89
4	**10**	Cs_2CO_3	24		0
5	**11**	Cs_2CO_3	24		0
6	**12**	Cs_2CO_3	24		0
7[c]	**9**	Cs_2CO_3	24	**8**	79

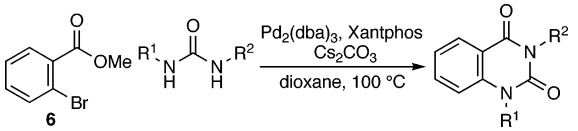
[a] Reaction conditions; substrate (1.0 equiv), urea (1.2 equiv), $Pd_2(dba)_3$ (0.5 mol %), ligand (1 mol %), base (2.0 equiv). [b] Isolated yields. [c] 5.0 mol % $Pd_2(dba)_3$, 10.0 mol % ligand.



structurally similar ligand DPEphos, and the two biphenyl ligands **11**[16] and **12**;[17] however, even when Cs_2CO_3 was used as base, no reaction was observed (entries 4−6). Finally, the simplest method to reduce the reaction times was to increase the catalyst loading from 1 mol % palladium to 10 mol % (entry 7).

With conditions for the synthesis of the parent heterocycle available, we next explored the scope of the urea coupling partner and the regioselectivity of the process (Table 2). The use of *N*,*N*′-dimethylurea led to a faster reaction with the desired product obtained in 90% yield after 24 h (entry 1).

Table 2. Scope of the Urea Component[a]



entry	R^1, R^2	time (h)	yield (%)[b]
1	Me, Me	24	90
2	H, Me	48	99
3	H, Bu	48	95
4	H, Oct	48	84
5	H, Cy	48	97
6	H, allyl	48	62
7	H, Bn	48	95
8	H, Ph	48	63

[a] Reaction conditions; substrate (1.0 equiv), urea (1.2 equiv), $Pd_2(dba)_3$ (2.5 mol %), ligand (5.0 mol %), base (2.0 equiv). [b] Isolated yields of pure regioisomer.

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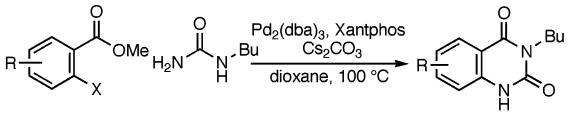
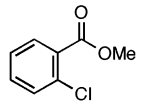
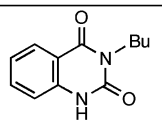
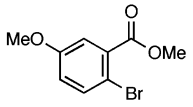
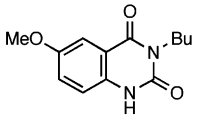
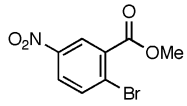
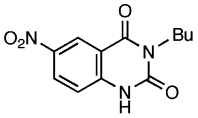
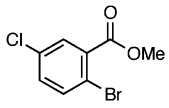
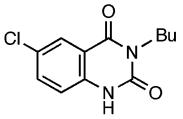
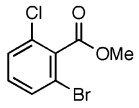
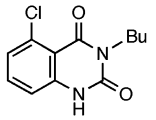
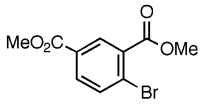
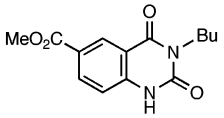
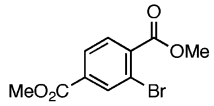
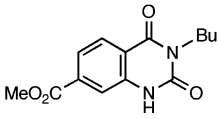
Table 3. Scope of the Halo Benzoate Component[a]



entry	substrate	product	yield (%)[b]
1[c]			33
2			72
3			92
4			85
5			68
6			99
7			95

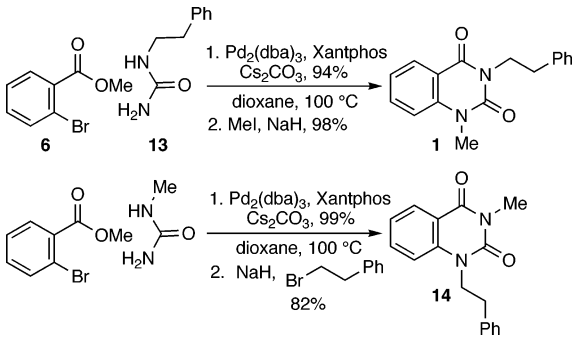
[a] Reaction conditions; substrate (1.0 equiv), urea (1.2 equiv), $Pd_2(dba)_3$ (2.5 mol %), ligand (5.0 mol %), base (2.0 equiv). [b] Isolated yields. [c] 2-(Dimethylamino)-2′-dicyclohexylphosphino-1,1′diphenyl employed as ligand (10.0 mol %).

When monoalkylated ureas were employed the reactions required 48 h to reach completion; methyl-, butyl-, octyl-, cyclohexyl-, allyl-, benzyl-, and phenyl-substituted ureas all performed well, delivering the quinazolinedione products in good yields (entries 2−8). In all of these examples the 3-alkyl regioisomer was obtained as the exclusive product. This was established by comparison with literature data, nOe studies, and by conversion to known compounds. We are confident that this selectivity arises from an initial arylation reaction followed by a ring-closing amidation. In addition, the arylation reaction occurs on the least hindered, unsubstituted *N*-atom of the urea.[18] In a control reaction we established that combination of bromobenzoate **6** with *N*,*N*-dimethylurea, under our standard reaction conditions, leads to formation of the *N*-arylated urea with the ester group remaining intact.

We next explored the variation possible in the benzoate component (Table 3). Although reaction of the *o*-chlorobenzoate substrate with our standard conditions delivered only trace amounts of the desired product, this could be increased to 33% by employing Buchwald's 2-(dimethylamino)-2′-dicyclohexylphosphine-substituted biphenyl ligand (entry 1).[19] Returning to the Br-substituted substrates we were pleased to find that both an electron-donating methoxy substituent and an electron-withdrawing nitro group could be readily incorporated (entries 2 and 3). The remainder of the examples serve to demonstrate that functionality suitable for modification of the heterocyclic products can be incorporated into the cyclization substrates; Cl substituents could be introduced at both the quinazolinedione 5- and 6-positions and methyl esters at both positions 6 and 7 (entries 4−7).

Finally, to demonstrate the utility of the quinazolinedione synthesis we prepared the simple natural product **1**, isolated from Mexican seed husks (Scheme 2).[5,8b] Tandem urea

Scheme 2. Synthesis of Natural Product **1** and Regioisomer **14**



arylation−ester amidation with bromobenzoate **6** and urea **13** delivered the 3-*N*-alkylquinazolinedione in 94% yield. Methylation with methyl iodide and sodium hydride provided the natural product. The regioisomeric compound (**14**) could also be readily prepared by simply employing *N*-methylurea for initial heterocycle formation and then alkylating with the indicated electrophile.

In conclusion, we have demonstrated an efficient one-step route to 3-alkyl quinazolinediones using *o*-bromobenzoates as substrates. Heterocycle formation involves tandem, regioselective, palladium-catalyzed arylation of a monoalkyl urea followed by an intramolecular amidation reaction. A variety of both functionalized ureas and benzoate coupling partners can be employed, allowing access to a diverse range of functionalized quinazolinedione products.

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Supporting Information Available: Experimental procedures and full characterization for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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