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Molybdenum-mediated synthesis of quinazolin-4(3*H*)-ones via cyclocarbonylation using microwave irradiation

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ABSTRACT

A new, efficient and practical synthesis of quinazolin-4(3*H*)-ones is reported via molybdenum-mediated cyclocarbonylation using microwave irradiation. These methods allow access to a wide range of quinazolin-4(3*H*)-ones in reasonable yields without the need for gaseous carbon monoxide and palladium catalysts. A range of reactions illustrating the wide scope of this chemistry was carried out and all proceeded in reasonable yields.

Quinazolin-4(3*H*)-ones are very important scaffolds in the field of medicinal chemistry possessing a diverse range of biological and pharmacological activity.[1] For example, compounds containing the quinazolin-4(3*H*)-one scaffold have shown promise as antibacterial,[2] antiinflammatory,[3] anticancer,[4] antihypertensive,[5] anticonvulsant,[6] and antimalarial[7] agents. There are numerous methods for the synthesis of quinazolin-4(3*H*)-ones in the literature,[8] however, the routes often require many steps or harsh reaction conditions resulting in low efficiency. Of direct relevance to the work presented here are: (1) synthesis of quinazolin-4(3*H*)-ones by the reaction of amines with carbodiimides derived from 2-aminobenzoates;[9] (2) synthesis from 2-iodoanilines with heterocumulenes or from *N*-(2-iodophenyl)-*N*′-phenyl-carbodiimides with nucleophiles via palladium-catalysed cyclocarbonylation.[8] Whilst these methods are efficient, they require long reaction times, and for cyclocarbonylation, high pressures of carbon monoxide gas, requiring specialised equipment.

We recently reported molybdenum-mediated carbonylation of aryl halides with nucleophiles to give carbonyl products under microwave irradiation.[10] Subsequently, Yamane reported a similar molybdenum-mediated carbamoylation of aryl halides under thermal conditions with sub-stoichiometric amounts of molybdenum carbonyl complexes.[11] Continuing our work in this area, in search of expedient and efficient methods to synthesise biologically active molecules, we now report the synthesis of quinazolin-4(3*H*)-ones via molybdenum-mediated cyclocarbonylation.

The required carbodiimides, prepared by literature procedures[8,9,12] were subjected to the reaction conditions shown in Table 1. Starting with an equimolar mixture of carbodiimide **1a**, butylamine, $Mo(CO)_6$ and $Et_4N{\cdot}Cl$ in 1,4-dioxane, an optimisation study of the reaction was performed with respect to time and temperature.[13] A reaction time of 2 h at 130 °C gave a single regioisomer **2** in 82% yield (Table 1, entry 1). To check for palladium contamination, ICP analysis of the reaction mixture was performed and palladium was not detected (limit of detection $<9.5 \times 10^{-9}$ mol %). Under these optimised conditions other primary amines, *iso*-propyl, benzyl and *tert*-butyl all performed well and gave **2** as a single regioisomer (Table 1, entries 2–4). Interestingly, anhydrous ammonia gave exclusively regioisomer **3** in 83% yield (Table 1, entry 5). The secondary amine, pyrrolidine gave the highest yield of product under these conditions (Table 1, entry 6). However, morpholine and piperidine required both higher temperature and extended reaction time to achieve modest yields (Table 1, entries 7–10). A low yield was obtained with aniline (Table 1, entry 11), which we suspect was due to slow formation of the intermediate guanidine and competing reaction of aniline with the molybdenum carbonyl complex. Gratifyingly, the yield was improved by the initial in situ formation of the guanidine prior to addition of $Mo(CO)_6$ and $NEt_4{\cdot}Cl$ (Table 1, entry 12). Using $Mo(CO)_6$ alone gave the product in reduced yield (Table 1, entry 13), although this yield was improved with further heating (Table 1, entry 14). Carbodiimide **1b** also performed well in the reaction (Table 1, entry 15). However, with benzylamine

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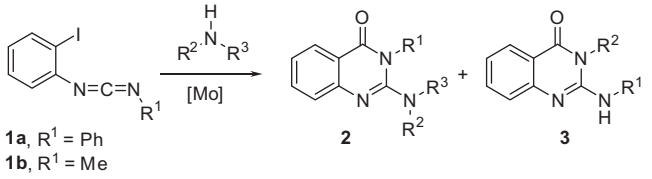
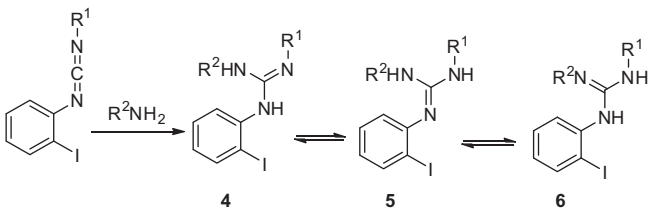
Table 1
Molybdenum-mediated cyclocarbonylation of carbodiimides **1a**–**b** with various amines[a]



Entry	R^1	R^2	R^3	Yield[b] (%)	
				2	**3**
1	Ph	*n*-Butyl	H	82	0
2	Ph	*iso*-Propyl	H	88	0
3	Ph	Benzyl	H	56	0
4	Ph	*tert*-Butyl	H	52	0
5	Ph	H	H	0	83
6	Ph	Pyrrolidine		92	
7	Ph	Morpholine		10	
8	Ph	Morpholine		55[c]	
9	Ph	Piperidine		<5	
10	Ph	Piperidine		54[c]	
11	Ph	Phenyl	H	10	0
12	Ph	Phenyl	H	56[d]	0
13	Ph	*n*-Butyl	H	32[e]	0
14	Ph	*n*-Butyl	H	47[f]	0
15	Me	Pyrrolidine		62	
16	Me	Benzyl	H	41	14[g]

[a] $Mo(CO)_6$ (0.5 mmol) and $NEt_4{\cdot}Cl$ (0.5 mmol), amine (0.5 mmol), carbodiimide **1** (0.5 mmol) and 1,4-dioxane (4 mL) were microwave heated in a sealed vial to 130 °C for 2 h.
[b] Isolated and purified.
[c] 150 °C for 4 h.
[d] Aniline (0.5 mmol) and carbodiimide (0.5 mmol) were sealed and microwave heated at 60 °C for 10 min, cooled and $Mo(CO)_6$ (0.5 mmol) and $NEt_4{\cdot}Cl$ (0.5 mmol) added, sealed and microwave heated to 130 °C for 2 h.
[e] $Mo(CO)_6$ (0.5 mmol), amine (0.5 mmol), carbodiimide **1** (0.5 mmol) and 1,4-dioxane (4 mL) were microwave heated in a sealed vial to 130 °C for 2 h.
[f] $Mo(CO)_6$ (0.5 mmol), amine (0.5 mmol), carbodiimide **1** (0.5 mmol) and 1,4-dioxane (4 mL) were microwave heated in a sealed vial to 150 °C for 4 h.
[g] Ratio **2**:**3**(3:1).

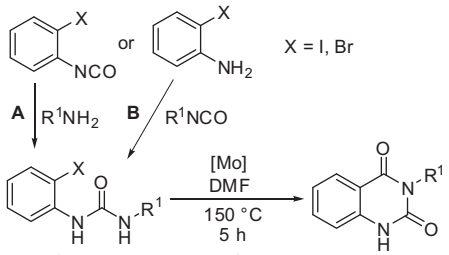
the product was isolated as an inseparable mixture of regioisomers (Table 1, entry 16). HPLC/MS analyses of the reaction mixtures prior to microwave heating confirmed that the cyclocarbonylation reaction proceeds via the in situ formation of tautomeric guanidines, **4**–**6** (Scheme 1). It is interesting to note that when R^1 is phenyl and R^2 is alkyl the reactions are regioselective. Preferential cyclisation of the guanidine intermediate occurs from an NH-aryl rather than an NH-alkyl group. Similar selectivity has been observed by others in the synthesis of 2-alkylamino-quinazolin-4(3*H*)-ones[9] and in the synthesis of benzimidazoles from mixed aryl/alkyl guanidines.[14] However, when R^1 is phenyl and R^2 is H (Table 1, entry 5) the regiochemistry was reversed and when R^1 is methyl and R^2 is alkyl (Table 1, entry 16) an inseparable mixture of products was obtained. We speculate that the regiochemical outcome of the reaction is determined by a combination of the intermediate guanidine geometry and steric effects.



Scheme 1. In situ formation of tautomeric guanidines from carbodiimides **1a** and **1b.**

To extend further this methodology to the synthesis of quinazoline-2,4-diones we examined the reactions shown in Table 2. Initially the required precursor ureas were synthesised and isolated via literature methods from 2-iodoaniline (route B).[15] Subsequent reactions were performed in one-pot from the precursor isocyanates without isolation of the intermediate ureas (route A). Initial optimisation of the reaction was performed in the microwave apparatus with respect to time and temperature using a 1:1 mixture of isolated urea **7a,** and $Mo(CO)_5Cl{\cdot}NEt_4$ in DMF.[16] A time of 5 h and temperature of 150 °C gave the required product in 65% yield (Table 2, entry 1). Using a 1:1 mixture of $Mo(CO)_6$ and $Et_4N{\cdot}Cl$ gave a similar result (Table 2, entry 2), whereas using $Mo(CO)_6$ alone gave the product in reduced yield (Table 2, entry 3). These reactions were repeated with a second urea, substrate **7c**, and an identical trend was seen where $Mo(CO)_6$ alone gave the lowest yield (Table 2, entries 4–6). Using route B, the amine and precursor isocyanate were stirred for 15 min in DMF at ambient temperature, before adding $Mo(CO)_5Cl{\cdot}NEt_4$ or a 1:1 mixture of $Mo(CO)_6$ and $Et_4N{\cdot}Cl$. Benzyl-, butyl-, phenyl- and cyclopentyl-amines all gave reasonable yields of product in this one-pot procedure (Table 2, entries 7–11). It is worth noting that all these reactions can be per-

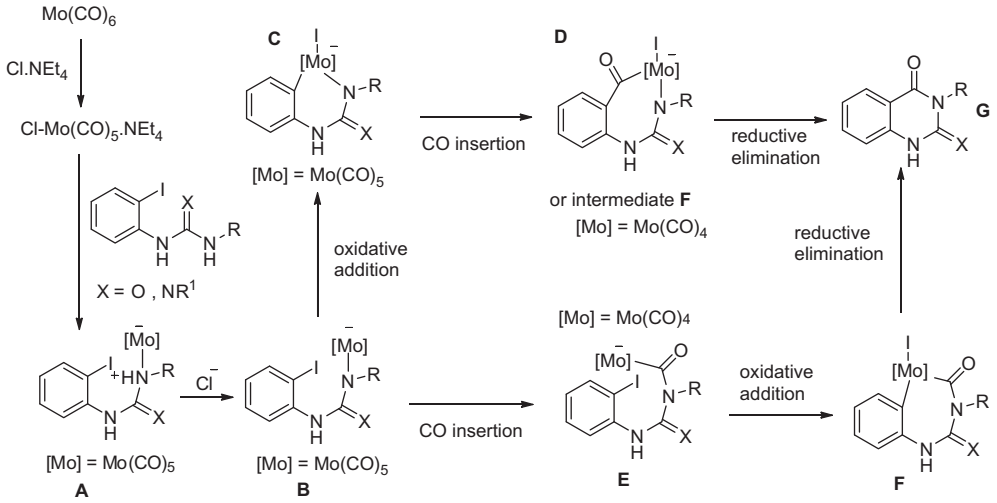
Table 2
Molybdenum-mediated cyclocarbonylation of aryl ureas **7a**–**g** via routes **A**[a] or **B**[b]



7a R^1 = Et, X = I, **7b** R^1 = Bu, X = I,
7c R^1 = Bn, X = I, **7d** R^1 = Ph, X = I,
7e R^1 = cPent, X = I, **7f** R^1 = Bu, X = Br,
7g R^1 = Bn, X = Br

Entry	Route	Urea	[Mo]-complex	Yield (%)[c]
1	**A**	**7a**	$Mo(CO)_5Cl{\cdot}NEt_4$	65
2	**A**	**7a**	$Mo(CO)_6 + Et_4N{\cdot}Cl$	64
3	**A**	**7a**	$Mo(CO)_6$	40
4	**A**	**7c**	$Mo(CO)_5Cl{\cdot}NEt_4$	58
5	**A**	**7c**	$Mo(CO)_6 + Et_4N{\cdot}Cl$	54
6	**A**	**7c**	$Mo(CO)_6$	40
7	**B**	**7c**	$Mo(CO)_5Cl{\cdot}NEt_4$	55
8	**B**	**7b**	$Mo(CO)_6 + Et_4N{\cdot}Cl$	75
9	**B**	**7b**	$Mo(CO)_5Cl{\cdot}NEt_4$	74
10	**B**	**7d**	$Mo(CO)_5Cl{\cdot}NEt_4$	53
11	**B**	**7e**	$Mo(CO)_5Cl{\cdot}NEt_4$	63
12	**A**	**7c**	$Mo(CO)_5Cl{\cdot}NEt_4$	40[d]
13	**B**	**7b**	$Mo(CO)_5Cl{\cdot}NEt_4$	41[d]
14	**B**	**7f**	$Mo(CO)_5Cl{\cdot}NEt_4$	47[e]
15	**B**	**7g**	$Mo(CO)_5Cl{\cdot}NEt_4$	30[e]

[a] [Mo]-complex (1 mmol) or $Mo(CO)_6$ (1 mmol) and $NEt_4{\cdot}Cl$ (1 mmol), urea **7** (1 mmol) and DMF (3 mL) were microwave heated in a sealed vial to 150 °C for 5 h.
[b] A mixture of arylisocyanate (1 mmol) and amine (1.2 mmol) in DMF (3 mL) was stirred for 15 min, $Mo(CO)_5Cl{\cdot}NEt_4$ (1 mmol) or $Mo(CO)_6$ (1 mmol) and $NEt_4{\cdot}Cl$ (1 mmol) were added and microwave heated in a sealed vial to 150 °C for 5 h.
[c] Isolated and purified
[d] $Mo(CO)_5Cl{\cdot}NEt_4$ (0.25 mmol) was used and reactions heated in the microwave for 10 h.
[e] Heated in the microwave for 10 h.



Scheme 2. Speculative mechanism for the synthesis of quinazolin-4(3*H*)-ones via molybdenum-mediated cyclocarbonylation.

formed with sub-stoichiometric amounts of $Mo(CO)_5Cl{\cdot}NEt_4$ although the yields of product are reduced and longer reaction times are required for complete consumption of the starting materials (Table 2, entries 12 and 13). Further work to identify the optimal ratio of [Mo]-complex and reaction concentration is on-going. This methodology was applicable to aryl bromides, although the yields were reduced and longer reaction times were required (Table 2, entries 14 and 15). In all these reactions we saw no evidence of intramolecular cyclisation via the urea oxygen to give 4*H*-benzo[*d*][1,3]oxazin-4-one products which we have observed when performing this urea cyclisation under standard palladium-catalysed carbonylation conditions using carbon monoxide gas.[17]

In both of the outlined reactions, we speculate that urea and guanidine decomposition is a competing reaction at high temperatures and the lower yields obtained using $Mo(CO)_6$ compared to the $Mo(CO)_5Cl{\cdot}NEt_4$ complex are due to the fact that the chloride ligand in $Mo(CO)_5Cl{\cdot}NEt_4$ is more readily displaced by the urea or guanidine nitrogen than a CO ligand in $Mo(CO)_6$ (see proposed mechanism discussed below).

The mechanism of these reactions is unclear at present, but one can speculate on possible pathways (Scheme 2).[18] In our previous work we demonstrated that $Et_4N{\cdot}Cl$ readily displaces a CO ligand from $Mo(CO)_6$ to give $Mo(CO)_5Cl{\cdot}NEt_4$ and this complex reacts readily with nitrogen nucleophiles.[10] Thus we postulate that intermediate **B** could be generated in the reaction. This could then undergo oxidative-addition followed by CO insertion to give **D**. Reductive elimination furnishes product **G**. Alternatively intermediate **B** could undergo CO insertion, to give **E**, followed by oxidative-addition to give intermediate **F**. Once again reductive elimination would give the product.

It should be noted that we cannot rule out direct oxidative-addition to the aryl halide of a molybdenum species followed by CO insertion to generate an acyl molybdenum species in an analogous manner to palladium-catalysed cyclocarbonylation.[8] However, when we heated a 1:1 mixture of iodobenzene and $Mo(CO)_6$ in 1,4-dioxane in a microwave at 150 °C for 1 h we were unable to detect any reaction and iodobenzene remained intact.

In summary, we have developed an efficient and practical strategy for the synthesis of quinazolin-4(3*H*)-ones via molybdenum-mediated cyclocarbonylation. These methods allow access to a wide range of quinazolin-4(3*H*)-ones in reasonable yield without the need for gaseous carbon monoxide and palladium catalysts. The methods are ideally suited for parallel synthesis and automation often required in modern drug discovery. Further development of the sub-stoichiometric versions of these reactions is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.052.

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