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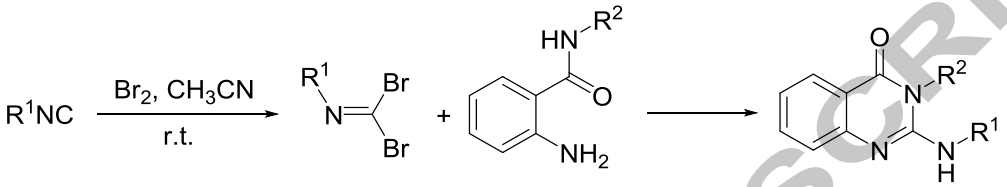

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An Efficient Metal-free Synthesis of 2-Amino-Substituted-4(3*H*)-Quinazolinones

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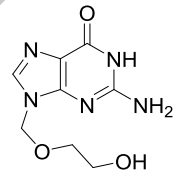
ABSTRACT

2-Amino-substituted-4(3*H*)-quinazolinones have been synthesized *via* an efficient metal-free reaction between 2-aminobenzamide derivatives and carbonimidic dibromides. The reaction proceeds in the presence of K_2CO_3 affording cyclized products in good to excellent yields.

1. Introduction

The fascinating reactivity of isocyanides in different reactions offers a powerful tool for the synthesis of heterocycles.[1] This utility arises from the dual nucleophilicity and electrophilicity of isocyanides which leads to a variety of interesting scaffolds. The association of isocyanides in various named reactions such as Ugi,[2] Passerini,[3] Nef[4] as well as insertion reactions[5] form part of the reported applications of isocyanides in organic synthesis. Moreover, isocyanides can be converted into dihalogen isocyanides under the action of chlorine or bromine, providing new insights for further cyclization in a one-pot manner.[6] These stable intermediates have been applied to the construction of cyclic compounds[7] and simple organic molecules (e.g., isocyanates,[8] isothiocyanates,[9] and carbodiimides[10]) which are classified as important substrates in the synthesis of heterocycles.



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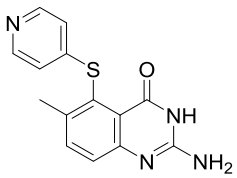

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Figure 1. Structures of acyclovir **1** and nolatrexed **2**.

Quinazolinones are found as a privileged structure in numerous natural products exhibiting diverse biological properties.[11] Meanwhile, 2-amino-substituted-4(3*H*)-quinazolinone, demonstrates antifungal activities against *Gibberella zeae* and *F. oxysporum*, and antibacterial activities against *Ralstonia solanacearum* and *Xanthomonas oryzae*.[12] It is worth mentioning that this core is an integral part of nolatrexed[13] and acyclovir[14] which are employed for the treatment of cancer and herpes simplex virus infections respectively. Methods for the preparation of 2-amino-substituted-4(3*H*)-quinazolinones utilizing transition metals such as palladium-catalyzed isocyanide insertion[15] or molybdenum-mediated cyclocarbonylation have been reported.[16] In another approach, higher temperatures were needed in a multi-step protocol, starting from anthranilic acid.[17] Regarding the drawbacks of the above-mentioned methods such as the toxicity of metal catalysts and higher temperatures, the development of novel, metal-free and mild methodologies has added interest for the construction of 2-amino-substituted-4(3*H*)-quinazolinones with possible pharmaceutical values.

In line with recently reported applications of 2-amino benzamides in the synthesis of new heterocyclic compounds,[18] herein, an efficient reaction of these derivatives with carbonimidic dibromide was developed.

First, we began our study with *in situ* preparation of carbonimidic dibromide **6**, using 1 equiv. of cyclohexyl isocyanide and 1 equiv. of bromine in acetonitrile at room temperature. Next, K_2CO_3 and 2-amino-*N*-phenyl benzamide were added and heated at reflux for 8 h. 2-Amino-*N*-substituted benzamide derivatives were obtained as a solid *via* the

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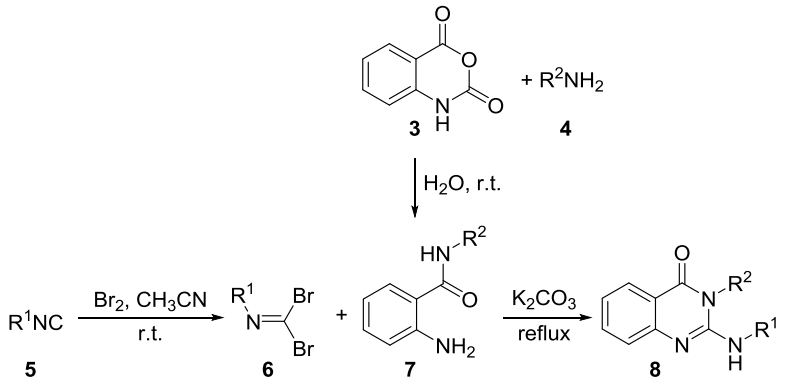

Scheme 1. One-pot, two-step synthetic route for the synthesis of quinazolin-4(3*H*)-ones.

reaction of isatoic anhydride and aryl or heteroaryl primary amines in water.[19]

As depicted in Table 1, we surveyed different inorganic and organic bases such as Et_3N, DABCO, *t*-BuOK, *t*-BuONa, and K_2CO_3 to optimize the model reaction. K_2CO_3 was found to be superior in terms of isolated yields (Table 1, entries 1-5). The presence of base was necessary for reaction progression due to the need for HBr scavenging (Table 1, entry 6). Among different amounts of K_2CO_3 tested, 2.5 equiv. furnished better results for the preparation of **8a**, giving 73 % yield (Table 1, entries 7, 8).

Table 1. Optimization of the reaction conditions.

Entry	Base (equiv.)[a]	Yield %[b]
1	K_2CO_3 (2)	71
2	Et_3N (2)	41
3	DABCO (2)	56
4	*t*-BuOK (2)	29
5	*t*-BuONa (2)	58
6	-	trace
7	K_2CO_3 (2.5)	73
8	K_2CO_3 (3)	66

[a]All reactions conducted at reflux in acetonitrile.

[b]Isolated yields.

Next, the scope of the reaction was examined using cyclohexyl and *tert*-butyl isocyanides and different 2-amino-*N*-substituted benzamide derivatives. Interestingly, heterocyclic rings such as furan and electron-rich and electron-deficient substituents at the *meta* or *para* position of the phenyl group afforded the target compounds in good to excellent isolated yields (Table 2).

In conclusion, a straightforward one-pot, two-step strategy for the synthesis of 2-amino-substituted quinazolin-4(3*H*)-ones was investigated. This transformation proceeds *via* the formation of two new C-N bonds in a sequential manner. Carrying out this reaction *via* a simple one-pot procedure and under metal-free condition simplifies this reaction and introduces a new methodology which is amenable for the synthesis of libraries of important bioactive compounds.

Table 2. The synthesis of 2-amino-substituted quinazolin-4(3*H*)-ones **8a-8i** (Scheme 1)[a]

Entry	product	R^1	R^2	Yield (%)[b]
1	**8a**	cyclohexyl	C_6H_5	73
2	**8b**	cyclohexyl	$C_6H_5CH_2$	76
3	**8c**	cyclohexyl	4-$MeOC_6H_4CH_2$	85
4	**8d**	cyclohexyl	2-$ClC_6H_4CH_2$	69
5	**8e**	cyclohexyl	4-$ClC_6H_4CH_2$	72
6	**8f**	cyclohexyl	Furan-2-yl-methyl	70
7	**8g**	*tert*-butyl	$C_6H_5CH_2$	78
8	**8h**	*tert*-butyl	4-$MeC_6H_4CH_2$	80
9	**8i**	*tert*-butyl	4-$FC_6H_4CH_2$	71

[a] General condition: **5** (1 mmol), Br_2 (1 mmol), room temperature, 10 min. Then, **7** (1 mmol) and K_2CO_3 (2.5 mmol) were added, reflux, 8 h.
[b] Isolated yields.

Acknowledgments

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19. General procedure for the synthesis of *2-(Cyclohexylamino)-3-phenylquinazolin-4(3H)-one* (**8a)**: Bromine (1 mmol) was added to a stirred solution of cyclohexyl isocyanide (1 mmol) in acetonitrile (5 mL). After 10 minutes, K_2CO_3 (2.5 mmol) and 2-amino-*N*-phenylbenzamide (1 mmol) were added and the mixture heated at reflux for 8h. After this time, the solvent was removed under reduced pressure and the residue purified by column chromatography (petroleum ether/ethyl acetate 10:1) to obtain **8a** as a white solid. Yield: 73%, White solid. m.p. 156–158 °C; IR (KBr) (ν_{max}, cm^{-1}): 3284, 2917, 2844, 1732, 1624, 1412, 1017; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.95 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 7.23-7.33 (m, 6H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 7.5 Hz, 1H), 3.96 (m, 1H), 1.83-1.85 (m, 2H, cyclohexyl), 1.58-1.70 (m, 3H, cyclohexyl), 1.27-1.31 (m, 5H, cyclohexyl); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 162.0, 149.3, 149.1, 136.4, 134.2, 128.4, 127.1, 126.7, 126.6, 124.5, 121.6, 116.1, 42.8, 31.9, 25.3, 24.7; Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16; Found: C, 75.48; H, 6.19; N, 12.99.