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Efficient Synthesis of 2-Methylenethiazolo[2,3-*b*]quinazolinone Derivatives

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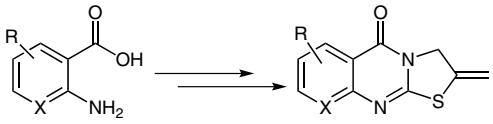

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Abstract Substituted *o*-amino-*N*-(prop-2-yn-1-yl) aromatic amides easily reacted with carbon disulfide (CS_2) in the presence of potassium hydroxide (KOH) in EtOH under reflux conditions. Cyclization reaction followed by a favored 5-*exo*-dig ring closure afforded 2-methylenethiazolo[2,3-*b*]quinazolinone derivatives in good yields.

Key words 2-methylene-thiazolo[2,3-*b*]quinazolinones, propargylamine, carbon disulfide, fused quinazolinone, 5-*exo*-dig

Quinazolinone derivatives are a vital structural motif in a variety of biologically active compounds.[1] Their valuable properties, such as antitumor,[2] anticonvulsant,[3] anti-inflammatory,[4] and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitory activities,[5] have attracted a great deal of attention. Also, they have been well known as peptidomimetic scaffold.[6] Among the various quinazolinones, fused derivatives possess an extensive array of biological activities. At this juncture, thiazolo[2,3-*b*]quinazolinones are found in a variety of bioactive compounds in medicinal chemistry. Anticancer and antimicrobial,[7] antihypertensive,[8] as well as herbicidal activities[9] have been reported in the literature. Accordingly, there has been significant interest in developing synthetic methods for their efficient and user-friendly construction.

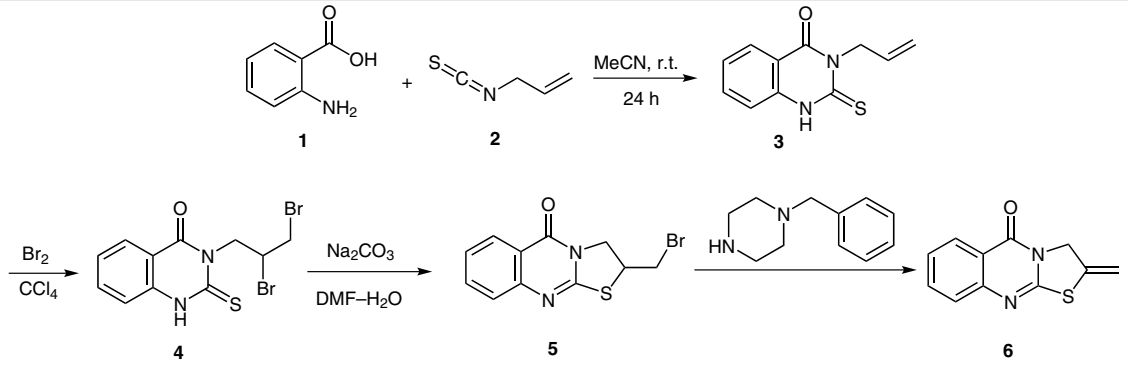
In spite of the important biological properties of thiazolo[2,3-*b*]quinazolinone, the literature lacks various reports on the practical library-based synthetic procedures. Previously, some derivatives were prepared using condensation reaction between allyl isothiocyanate and different anthranilic acids followed by the bromination of the resulted 3-allyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one derivatives.[10,11]

Later, as shown in Scheme 1, Shiau et al.[12] investigated the same strategy with more details only for the synthesis of 2-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**6**). The synthetic route was started from the reaction of anthranilic acid (**1**) and allyl isothiocyanate (**2**). The obtained product, 3-allyl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**3**), reacted with Br_2 and CCl_4 to give 3-(2,3-dibromopropyl)-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**4**) which was transformed to 2-(bromomethyl)-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**5**) in the presence of sodium carbonate in DMF–H_2O. Finally, the reaction of **5** with benzylpiperazine afforded 2-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**6**, Scheme 1).

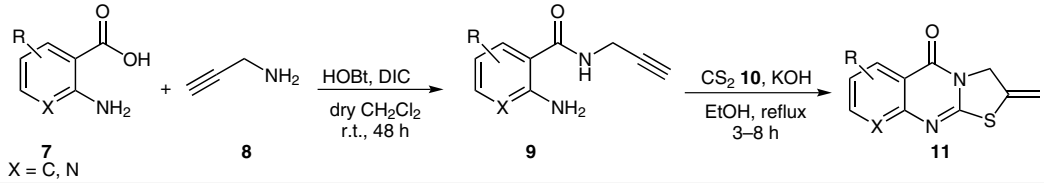
Herein, in continuation of our efforts to synthesize novel heterocycles,[13] we focused on the preparation of various 2-methylene-thiazolo[2,3-*b*]quinazolinones **11** starting from different 2-amino benzoic acids **7** (Scheme 2). For this purpose, various substituted *o*-amino-*N*-(prop-2-yn-1-yl) aromatic amides **9** were easily prepared by the reaction of 2-aminobenzoic acids **7** and propargylamine (**8**) in the presence of hydroxybenzotriazole (HOBt) and *N*,*N*′-diisopropylcarbodiimide (DIC) in anhydrous CH_2Cl_2 according to the procedure reported by Jablonski et al.[14] Then, the cyclization reaction of compounds **9** was comprehensively investigated.

Alkynes are versatile building blocks in organic transformations, and the intramolecular addition of a heteronucleophile such as oxygen, nitrogen, and sulfur to triple bond leads to the formation of heterocyclic rings.[15]

Usually these reactions need to be activated in the presence of an electrophilic reagent.[16] According to Baldwin's rules,[17] the oxygen and nitrogen cyclization are usually controllable. It is clear that the particular properties of sulfur, such as larger atomic size and greater polarizability, leads to stronger nucleophilicity and low regioselectivity.



Scheme 1 Synthesis of 2-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**6**)[12]



Scheme 2 Synthesis of 2-methylene-thiazolo[2,3-*b*]quinazolinone derivatives **11**

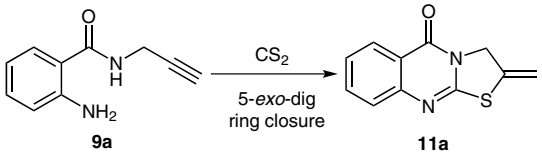
Recently, we successfully reported the synthesis of benzoxazepino[4,5-*a*]quinazolinones through base-promoted 7-*exo*-dig hydroamination of 3-substituted 2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones in the absence of transition-metal catalysts.[13b] In this study, we focused on the intramolecular cyclization of substituted *o*-amino-*N*-(prop-2-yn-1-yl) aromatic amides **9** in the reaction with CS_2 (**10**) to obtain the title compounds **11** (Scheme 2).

Hence, we selected 2-amino-*N*-(prop-2-yn-1-yl)benzamide (**9a**) as a model substrate to react with CS_2 (**10**) and examined various conditions including different temperature, bases/reagents, and solvents (Table 1). Table 1 shows that utilizing KOH in EtOH under reflux conditions afforded product **11a** in good yield (Table 1, entries 3 and 4).

Also, it was revealed that the corresponding product was formed when the reaction mixture was heated at the boiling point of the solvent. According to our results, an equivalent amount of base was sufficient, and higher amounts did not improve the yield of reaction.

With these results in hand, various 2-methylene-thiazolo[2,3-*b*]quinazolinones **11a**–**h** were prepared using different substituted *o*-amino-*N*-(prop-2-yn-1-yl) aromatic amides **9**. All substrates possessing electron-rich as well as electron-poor substituents underwent potassium hydroxide promoted cyclization reaction with CS_2 followed by 5-*exo*-dig ring closure to give the corresponding products **11** in relatively short reaction time (3–8 h), and commonly good yields were achieved (Scheme 2, Table 2).

Table 1 Investigation of Various Conditions for the Reaction of **9a** to Obtain the Corresponding Product **11a**

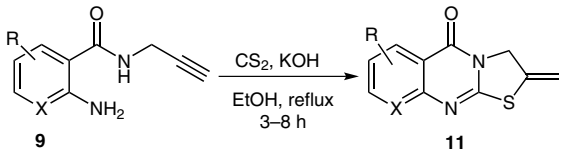


Entry	Solvent	Base (equiv)	Temp (°C)	Yield (%)[a]
1	EtOH	–	r.t.	0
2	EtOH	KOH (1)	r.t.	trace
3	EtOH	KOH (1)	reflux	85
4	EtOH	KOH (2)	reflux	85
5	EtOH	NaOH (1)	reflux	70
6	EtOH	Et_3N (1)	reflux	5
7	EtOH	K_2CO_3 (1)	reflux	30
8	EtOH	piperidine (1)	reflux	10
9	EtOH	L-proline (1)	reflux	15
10	DMF	KOH (1)	reflux	65
11	PhMe	KOH (1)	reflux	50
12	1,4-dioxane	KOH (1)	reflux	60

[a] Isolated yields.

All products were characterized using IR and NMR spectroscopy, and all data confirmed the structures of the synthesized compounds.

Table 2 Synthesis of 2-Methylene-thiazolo[2,3-*b*]quinazolinones **11**[19]



Entry	R	X	Product **11**	Mp (°C)	Time (h)	Yield (%)[a]
1	H	C	**11a**	220–222 (lit.11 202)	3	85
2	5-Me	C	**11b**	160–162 (lit.11 150)	4	80
3	4,5-$(MeO)_2$	C	**11c**	221–223	5	75
4	4-Cl	C	**11d**	170–171 (lit.18 167)	4	70
5	5-Cl	C	**11e**	190–192 (lit.10 193)	4	70
6	C_4H_4 (3-amino-2-naphthoic acid)	C	**11f**	190–192	7	65
7	4-O_2N	C	**11g**	180–181	8	50
8	H	N	**11h**	180–182	8	45

[a] Isolated yields.

In conclusion, a practical and easy approach was established for the preparation of 2-methylene-thiazolo[2,3-*b*]-quinazolinones through the potassium hydroxide promoted cyclization reaction of substituted *o*-amino-*N*-(prop-2-yn-1-yl) aromatic amides and CS_2 followed by 5-*exo*-dig ring closure in EtOH under reflux conditions. Various benefits such as easy workup and lack of time-consuming purification steps make this work useful for organic as well as medicinal chemists to develop novel thiazoloquinazolinone-based drugs.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379499.

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(19) **Synthesis of 2-Methylene-thiazolo[2,3-*b*]quinazolinone Derivatives 11 – General Procedure**
A mixture of substituted *o*-amino-*N*-(prop-2-yn-1-yl) aromatic amides **9** (1 mmol), CS_2 (**10**, 2 mmol), and KOH (1 mmol) in EtOH (8 mL) was heated at reflux for 3–8 h. After completion of reaction (checked by TLC), the reaction mixture was cooled to r.t. and poured into cold H_2O. The precipitate was filtered off to obtain pure products **11** with no need for further purification.
2-Methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (11a)
Yield 0.18 g (85%); white solid; mp 220–222 °C (lit.[11] 202 °C). IR (KBr): 2937, 1665, 1582, 1553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.12 (t, *J* = 2.4 Hz, 2 H, CH_2), 5.37 (q, *J* = 2.4 Hz, 1 H, =CH_2), 5.50 (q, *J* = 2.4 Hz, 1 H, =CH_2), 7.42 (td, *J* = 7.6, 0.8 Hz, 1 H, H_7), 7.56 (dd, *J* = 7.6, 0.8 Hz, 1 H, H_9), 7.72 (td, *J* = 7.6, 1.5 Hz, 1 H, H_8), 8.22 (dd, *J* = 7.6, 1.5 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.2, 108.3, 119.3, 126.2, 126.3, 126.6, 133.1, 134.8, 148.8, 158.1, 159.9. Anal. Calcd for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95. Found: C, 60.87; H, 3.58; N, 13.14.
7-Methyl-2-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (11b)
Yield 0.18 g (80%); deep yellow solid; mp 160–162 °C (lit.[11] 150 °C). IR (KBr): 1669, 1621, 1581 m^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 5.11 (t, *J* = 2.4 Hz, 2 H, CH_2), 5.35 (q, *J* = 2.4 Hz, 1 H, =CH_2), 5.48 (q, *J* = 2.4 Hz, 1 H, =CH_2), 7.45 (d, *J* = 8.4 Hz, 1 H, H_9), 7.53 (dd, *J* = 8.4, 1.6 Hz, 1 H, H_8), 8.00 (s, 1 H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 54.2, 108.1, 119.0,

126.0, 126.1, 133.3, 136.1, 136.4, 146.8, 157.0, 159.9. Anal. Calcd for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.41; H, 4.52; N, 11.97.

7,8-Dimethoxy-2-methylene-2*H*-thiazolo[2,3-*b*]quinazolin-5(3*H*)-one (11c)

Yield 0.21 g (75%); deep yellow solid; mp 221–223 °C. IR (KBr): 1672, 1605, 1580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 5.12 (t, *J* = 2.4 Hz, 2 H, CH_2), 5.35 (q, *J* = 2.4 Hz, 1 H, =CH_2), 5.48 (q, *J* = 2.4 Hz, 1 H, =CH_2), 6.98 (s, 1 H, H_9), 7.52 (s, 1 H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.3, 56.2, 56.3, 105.5, 106.9, 108.1, 117.2, 133.4, 145.2, 148.5, 155.1, 156.4, 159.4. Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14. Found: C, 56.34; H, 4.50; N, 9.96.

8-Chloro-2-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (11d)

Yield 0.17 g (70%); off-white solid; mp 170–171 °C (lit.[18] 167 °C). IR (KBr): 2918, 1685, 1602, 1568 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.27 (t, *J* = 1.9 Hz, 2 H, CH_2), 5.37 (q, *J* = 1.9 Hz, 1 H, =CH_2), 5.61 (q, *J* = 1.9 Hz, 1 H, =CH_2), 7.37 (dd, *J* = 8.8, 2.0 Hz, 1 H, H_7), 7.62 (d, *J* = 2.0 Hz, 1 H, H_9), 8.27 (d, *J* = 8.8 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6, 115.2, 117.2, 123.3, 125.5, 125.8, 128.4, 149.0, 157.6, 159.5, 163.8. Anal. Calcd for $C_{11}H_7ClN_2OS$: C, 52.70; H, 2.81; N, 11.17. Found: C, 52.91; H, 2.68; N, 10.92.

7-Chloro-2-methylene-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (11e)

Yield 0.17 g (70%); white solid; mp 192–192 °C (lit.[10] 193 °C). IR (KBr): 2915, 1681, 1609, 1574 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.11 (s, 2 H, CH_2), 5.37 (d, *J* = 2.0 Hz, 1 H, =CH_2), 5.50 (d, *J* = 2.0 Hz, 1 H, =CH_2), 7.60 (d, *J* = 7.1 Hz, 1 H, H_9), 7.62 (dd, *J* = 7.1, 2.0 Hz, 1 H, H_8), 8.27 (d, *J* = 2.0 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.2, 108.6, 117.1, 123.6, 126.1, 127.8, 130.8, 135.1, 146.7, 157.2, 158.5. Anal. Calcd for $C_{11}H_7ClN_2OS$: C, 52.70; H, 2.81; N, 11.17. Found: C, 52.57; H, 2.93; N, 11.28.

2-Methylene-2,3-dihydro-5*H*-benzo[*g*]thiazolo[2,3-*b*]quinazolin-5-one (11f)

Yield 0.17 g (65%); yellow solid; mp 190–192 °C. IR (KBr): 1628, 1573, 1401 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.13–5.15 (m, 2 H, CH_2), 5.37–5.38 (m, 1 H, =CH_2), 5.50–5.51 (m, 1 H, =CH_2), 7.52 (t, *J* = 6.5 Hz, 1 H, H_9), 7.62 (t, *J* = 6.5 Hz, 1 H, H_8), 7.98 (d, *J* = 6.5 Hz, 1 H, H_{10}), 8.00 (s, 1 H, H_{11}), 8.07 (d, *J* = 6.5 Hz, 1 H, H_7), 8.13 (s, 1 H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9, 108.1, 116.8, 123.1, 123.6, 125.8, 126.2, 128.3, 128.6, 128.7, 128.8, 129.4, 137.0, 163.2, 163.6. Anal. Calcd for $C_{15}H_{10}N_2OS$: C, 67.65; H, 3.78; N, 10.52. Found: C, 67.83; H, 3.57; N, 10.37.

2-Methylene-8-nitro-2*H*-thiazolo[2,3-*b*]quinazolin-5(3*H*)-one (11g)

Yield 0.13 g (50%); yellow solid; mp 180–182 °C. IR (KBr): 1669, 1535, 1613, 1488, 1350 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 5.12 (t, *J* = 1.9 Hz, 2 H, CH_2), 5.35 (q, *J* = 1.9 Hz, 1 H, =CH_2), 5.48 (q, *J* = 1.9 Hz, 1 H, =CH_2), 6.49 (dd, *J* = 1.7 Hz, 1 H, H_9), 6.66 (dd, *J* = 6.9, 1.7 Hz, 1 H, H_7), 7.72 (d, *J* = 6.9 Hz, 1 H, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.8, 105.9, 108.2, 114.1, 127.3, 133.3, 150.3, 154.5, 156.7, 157.7, 158.4. Anal. Calcd for $C_{11}H_7N_3O_3S$: C, 50.57; H, 2.70; N, 16.08. Found: C, 50.39; H, 2.57; N, 15.87.

2-Methylene-2,3-dihydro-5*H*-pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-one (11h)

Yield 0.10 g (45%); deep yellow solid; mp 180–182 °C. IR (KBr): 2915, 1681, 1609 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 5.22 (t, *J* = 1.5 Hz, 2 H, CH_2), 5.63 (q, *J* = 1.5 Hz, 1 H, =CH_2), 5.65 (q, *J* = 1.5 Hz, 1 H, =CH_2), 6.60 (dd, *J* = 6.2, 3.8 Hz, 1 H, H_7), 8.04 (dd, *J* = 6.2, 1.5 Hz, 1 H, H_6), 8.17 (dd, *J* = 3.8, 1.5 Hz, 1 H, H_8). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 51.9, 105.5, 111.8, 120.3, 120.9, 123.3, 140.0, 153.4, 159.7, 168.6. Anal. Calcd for $C_{10}H_7N_3OS$: C, 55.29; H, 3.25; N, 19.34. Found: C, 55.42; H, 3.36; N, 19.52.