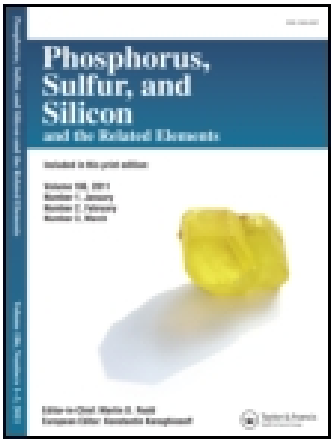

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Regioselective Syntheses of 1-Aryl-substituted-5H-[1,3]thiazolo[3,2-a]quinazoline-5-ones During Sonogashira Coupling

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REGIOSELECTIVE SYNTHESES OF 1-ARYL-SUBSTITUTED-5*H*-[1,3]THIAZOLO[3,2-*a*]QUINAZOLINE-5-ONES DURING SONOGASHIRA COUPLING

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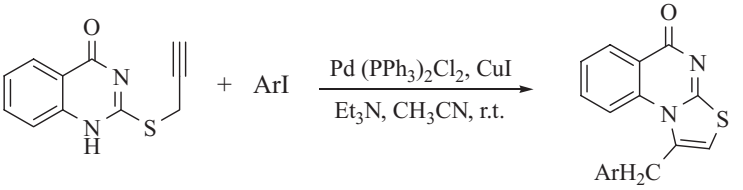
GRAPHICAL ABSTRACT



Abstract *Reaction of 2-mercaptopropargylquinazoline-4-one with various aryliodides catalyzed by Pd–Cu leads to the regioselective formation of 1-arylsubstituted-5H-[1,3]thiazolo-[3,2-a]quinazoline-5-ones.*

Keywords Aryl iodide; Pd-catalyzed; quinazoline; Sonogashira coupling; thiazoloquinazoline

INTRODUCTION

Quinazolinones are classes of fused heterocycles that are of considerable interest because of their diverse range of biological properties, such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive activities.[1–3] There has been considerable interest in transition metal–mediated cycloaddition reactions of aldehydes in organic synthesis,[4] especially those involving palladium.[5,6] Attempts to annulate intramolecularly onto alkynes using palladium have generally resulted in multiple alkyne insertion and subsequent cyclization back to the pre-existing aromatic ring.[7] Although a few multistep procedures[8] are available for the synthesis of carbocyclic[9] and heterocyclic compounds[10] using palladium, this annulation strategy has not been utilized for the syntheses of thiazoloquinazolinones.

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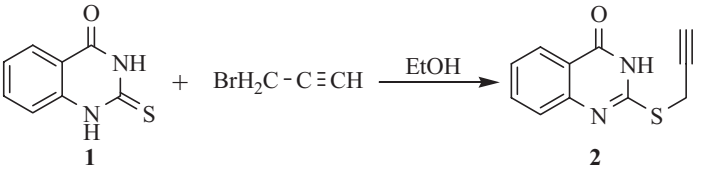
In continuation of our recent studies[11–13] on the palladium-catalyzed reactions of acetylenic substrates leading to heterocyclic compounds of biological significance, we became interested in the regioselective syntheses of substituted thiazoloquinazolinones using palladium–copper catalysis.

RESULTS AND DISCUSSION

When 2-propargylmercaptoquinazoline-4-one **2** was treated with aryl halides **3a–i** in triethylamine in the presence of bis(triphenylphosphin)palladium chloride and copper iodide, 1-aryl-substituted-5H-[1,3]thiazolo[3,2-*a*]quinazoline-5-ones **4** were obtained in moderate to good yields.

In the first step, 2-thioxo-2,3-dihydroquinazoline-4(1H)-one **1** was reacted with propargyl bromide to give the corresponding 2-propargylmercaptoquinazoline-4-one **2**.[14]



1 **2**

Heteroannulation of **2** through palladium–copper catalysis in the presence of aryl iodides **3a–i** led to the formation of either 1-aryl-substituted-5H-[1,3]thiazolo[3,2-*a*] quinazoline-5-ones **4** or 3-aryl-substituted-5H-[1,3]thiazolo[2,3-*b*]quinazoline-5-ones **5**.

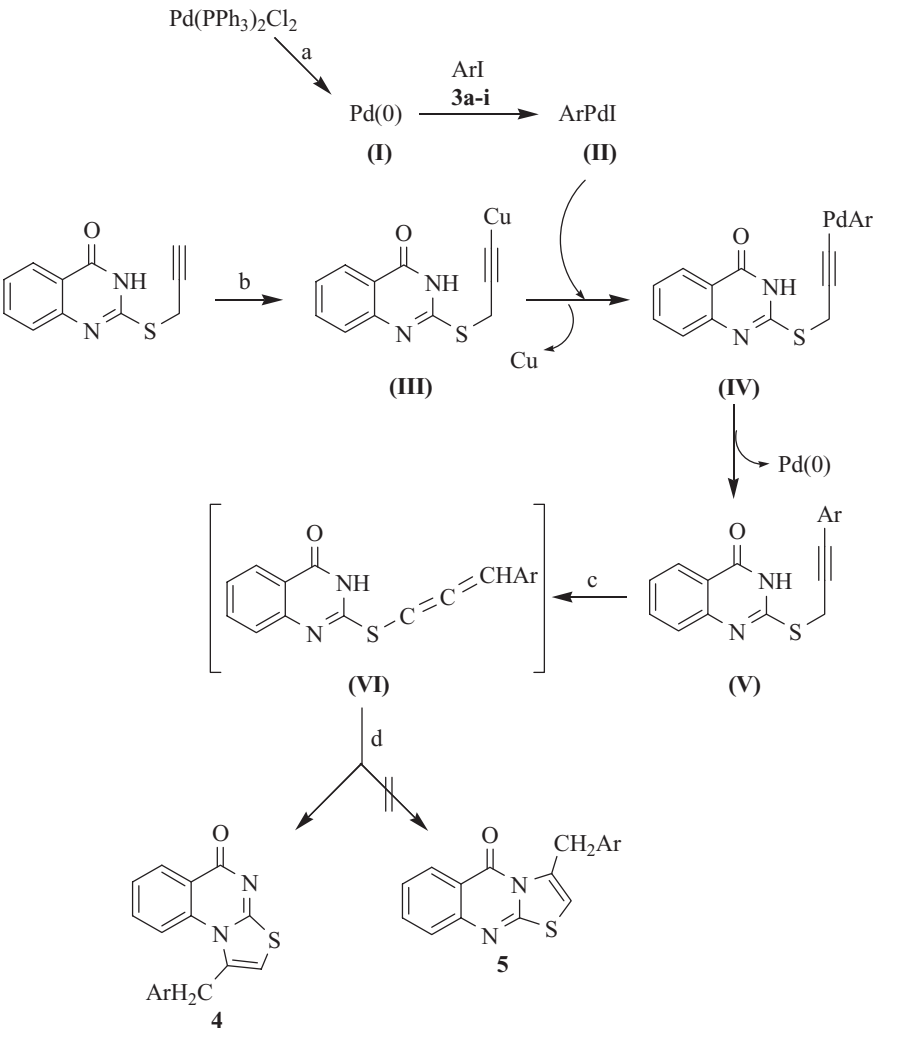
When **2** was treated with 2-nitro-1-iodobenzene **3a** and triethylamine in the presence of bis(triphenylphosphine)palladium chloride and copper iodide under an argon atmosphere in acetonitrile, a single compound was obtained, as detected by TLC. The ^{1}H NMR spectrum of the product showed one aromatic proton at δ 6.64, characteristic of a fused thiazole ring, as well as benzylic protons at δ 4.95.

Bis(triphenylphosphine)palladium chloride and cuprous iodide were found to be the catalyst and co-catalyst, respectively. Reactions were carried out with either just copper(I) iodide or just Pd(II) chloride, as the catalyst led to very poor yields of products. The results are tabulated in Table 1.

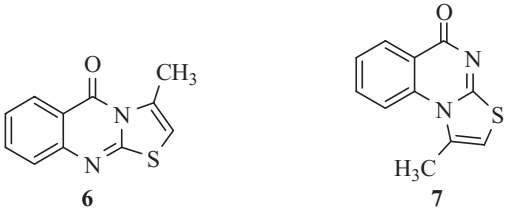
Mechanistically, either thiazolo[3,2-*a*]quinazoline-5-ones **4** or thiazolo[2,3-*b*] quinazoline-5-ones **5** are the possible products, as illustrated in Scheme 1: (a) formation of ArPdI **(II)** through oxidative addition of Pd(0) **(I)** to ArI[15]; (b) transmetallation of ArPdI with the Cu salt of **(III)**, generating the alkynyl palladium species **(IV)**; (c) reductive elimination of Pd(0) to yield the alkynes **(V)**; and (d) isomerization to the allenic intermediates[16] **(VI)**, which then cyclize to product **4** or **5**.

However, other mechanisms for this reaction are also plausible, for example, a 5-*exo*-dig cyclization may be triggered simply by the formation of an Ar–Pd(II) species followed by reduction, elimination, and isomerization. This type of cyclization has been observed for acetylenic lactams.[17]

The structures of **4** and **5** were established by comparing their spectra with those for the well-established compounds **6** (IR, $\upsilon_{(C=O)}$ 1695 cm^{-1}) and **7** (IR, $\upsilon_{(C=O)}$ 1640 cm^{-1})[14,18,19] (Scheme 2). The IR spectra for **4** or **5** were quite similar to that for **7**. Therefore, we can conclude that one-pot condensation, cyclization, and isomerization of acetylenic compounds regioselectively afford **4**.



Scheme 1 Proposed mechanism for the formation of either thiazolo[3,2-*a*]quinazoline-5-ones **4** or thiazolo[2,3-*b*]quinazoline-5-ones **5** at room temperature. Reagents and conditions: (a) Reduction of Pd(II) to Pd(0) with alkyne and Et_3N; (b) CuI, Et_3N; (c) isomerization to an allene with CuI, Et_3N; (d) nucleophilic attack on the allene (VI) to generate the product **4** or **5**.



Scheme 2

Table 1 Melting points and yields of 1-aryl-substituted-5H-[1,3]thiazolo[3,2-*a*]quinazoline-5-ones[a]

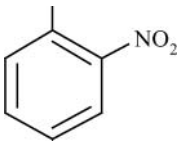
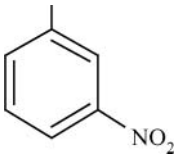
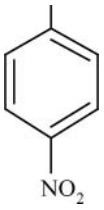
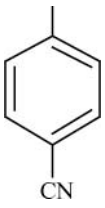
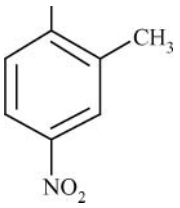
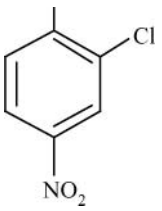
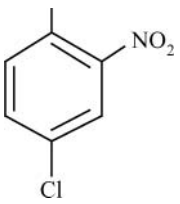
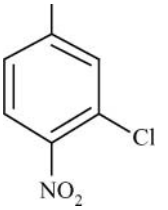
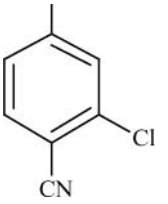
Entry	Ar	Mp (°C)	Yield (%)
4a		239–241	70
4b		252–254	72
4c		257–259	82
4d		230–232	75
4e		264–266	88
4f		244–246	85
4g		236–238	72

Table 2 Melting points and yields of 1-aryl-substituted-5H-[1,3]thiazolo[3,2-*a*]quinazoline-5-ones[a] *(Continued)*

Entry	Ar	Mp (°C)	Yield (%)
4h		255–257	65
4i		287–289	80

[a]Reaction reagents and conditions: **2** (1.3 mmol), **3a–i** (1 mmol), Et_3N (3 mmol), $Pd(PPh)_3Cl_2$ (0.03 mmol), CuI (0.06 mmol), and CH_3CN (6 mL) at room temperature for 12 h.

As shown in the Scheme 2, the allenic intermediates **(VI)** could undergo cyclization either around N1 or N3 of quinazoline. Due to the better nucleophilic power of the N1 site relative to the N3 site, cyclization occurs at the former one.

In conclusion, we have established the first successful one-pot condensation, regioselective cyclization, and isomerization for the syntheses of 1-arylsubstituted-5*H*-[1,3]thiazolo[3,2-*a*]quinazoline-5-ones. The method is easy to carry out under relatively mild conditions. Since there is no need for the use of any toxic reagents, it can be considered relatively eco-friendly. The process is thus amenable to the regioselective synthesis of thiazolo[3,2-*a*]quinazoline-5-ones.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. Elemental analyses were performed by Ferdowsi University, Mashhad, Iran.

Syntheses of 1-Aryl-substituted-5*H*-[1,3]thiazolo[3,2-*a*]quinazoline-5-ones 4a–i

A mixture of aryl iodide (1 mmol), $(PPh_3)_2PdCl_2$ (0.03 mmol), CuI (0.06 mmol), and triethylamine (3.0 mmol) was stirred in acetonitrile (6 mL) under an argon atmosphere. 2-Propargylmercaptoquinazoline-4-one **2** (1.3 mmol) was then added, and the mixture was stirred at room temperature for 12 h. The solid substance formed was filtered, washed with water, and recrystallized from ethanol (Table 1).

1-(2-Nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4a

IR (KBr, ν_{max} cm^{-1}): 1625, 1520, 1350, 1642. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.95 (s, 2H, CH_2), 6.64 (s, 1H, CH of thiazole), 7.52–7.79 (m, 4H, ArH), 8.01–8.20 (m, 2H, ArH), 8.23–8.42 (m, 2H, ArH), Anal. Calcd. for $C_{17}H_{11}N_3O_3S$: C, 60.52; H, 3.29; N, 12.46; S, 9.50. Found: C, 60. 38; H, 3.14; N, 12.32; S, 9.62%.

1-(3-Nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4b

IR (KBr, ν_{max} cm^{-1}): 1623, 1510, 1350. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.80 (s, 2H, CH_2), 6.70 (s, 1H, CH of thiazole), 7.33 (s, 1H, ArH), 7.54–7.65 (m, 3H, ArH), 8.04–8.23 (m, 4H, ArH), Anal. Calcd. for $C_{17}H_{11}N_3O_3S$: C, 60.52; H, 3.29; N, 12.46; S, 9.50. Found: C, 60. 41; H, 3.17; N, 12.57; S, 9.32%.

1-(4-Nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4c

IR (KBr, ν_{max} cm^{-1}): 1625, 1510, 1340. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.84 (s, 2H, CH_2), 6.66 (s, 1H, CH of thiazole), 7.53–7.65 (m, 4H, ArH), 8.04–8.15 (m, 2H, ArH), 8.25 (d, $J = 7.9$ Hz, 2H, ArH), Anal. Calcd. for $C_{17}H_{11}N_3O_3S$: C, 60.52; H, 3.29; N, 12.46; S, 9.50. Found: C, 60. 28; H, 3.13; N, 12.61; S, 9.24%.

1-(4-Cyanobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4d

IR (KBr, ν_{max} cm^{-1}): 2240, 1620. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.54 (s, 2H, CH_2), 6.75 (s, 1H, CH of thiazole), 7.50–7.72 (m, 4H, ArH), 7.80–8.97 (m, 2H, ArH), 8.15 (d, $J = 8.2$ Hz, 2H, ArH), Anal. Calcd. for $C_{18}H_{11}N_3OS$: C, 68.12; H, 3.49; N, 13.24; S, 10.10. Found: C, 68.30; H, 3.32; N, 13.43; S, 9.92%.

1-(2-Methyl-4-nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4e

IR (KBr, ν_{max} cm^{-1}): 1625, 1525, 1345. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 2.30 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 6.46 (s, 1H, CH of thiazole), 7.60–7.80 (m, 3H, ArH), 8.11–8.27 (m, 3H, ArH), 8.47 (d, $J = 8.2$ Hz, 1H, ArH), Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96; S, 9.13. Found: C, 61.70; H, 3.82; N, 11.81; S, 9.27%.

1-(2-Chloro-4-nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4f

IR (KBr, ν_{max} cm^{-1}): 1630, 1518, 1350. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.84 (s, 2H, CH_2), 6.78 (s, 1H, CH of thiazole), 7.60–7.68 (m, 2H, ArH), 7.85–8.05 (m, 2H, ArH), 8.23 (s, 1H, ArH), 8.32–8.52 (m, 2H, ArH), Anal. Calcd. for $C_{17}H_{10}ClN_3O_3S$: C, 54.92; H, 2.71; N, 9.54; S, 8.62. Found: C, 55.14; H, 2.83; N, 9.69; S, 8.45%.

1-(4-Chloro-2-nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4g

IR (KBr, ν_{max} cm^{-1}): 1627, 1525, 1350. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.89 (s, 2H, CH_2), 6.62 (s, 1H, CH of thiazole), 7.24 (d, $J = 7.6$ Hz, 1H, ArH), 7.63–7.84 (m, 2H, ArH), 7.95–8.14 (m, 2H, ArH), 8.21–8.28 (m, 1H, ArH), 8.47 (d, $J = 8.7$ Hz, 1H, ArH),

Anal. Calcd. for $C_{17}H_{10}ClN_3O_3S$: C, 54.92; H, 2.71; N, 9.54; S, 8.62. Found: C, 54.77; H, 2.61; N, 9.66; S, 8.40%.

1-(3-Chloro-4-nitrobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4h

IR (KBr, ν_{max} cm^{-1}): 1625, 1520, 1345. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.74 (s, 2H, CH_2), 6.78 (s, 1H, CH of thiazole), 7.53–7.72 (m, 4H, ArH), 8.05–8.20 (m, 3H, ArH), Anal. Calcd. for $C_{17}H_{10}ClN_3O_3S$: C, 54.92; H, 2.71; N, 9.54; S, 8.62. Found: C, 55.20; H, 2.88; N, 9.43; S, 8.76%.

1-(3-Chloro-4-cyanobenzyl)-5H-[1,3]thiazolo[3,2-a]quinazoline-5-one 4i

IR (KBr, ν_{max} cm^{-1}): 1628, 1510, 1340, 1642. ^1H NMR (500 MHz, $CDCl_3$ δ ppm): 4.86 (s, 2H, CH_2), 6.71 (s, 1H, CH of thiazole), 7.49–7.78 (m, 5H, ArH), 7.98–8.20 (m, 2H, ArH), Anal. Calcd. for $C_{18}H_{10}ClN_3OS$: C, 61.45; H, 2.87; N, 11.94; S, 9.11. Found: C, 61.68; H, 3.02; N, 12.14; S, 9.30%.

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