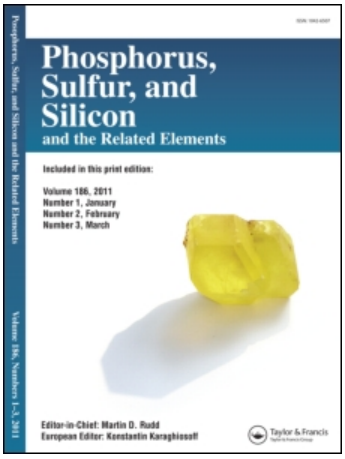

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Heteroannulation Through Palladium Catalysis: A Novel Cyclization Leading to Regioselective Synthesis of 3-Substituted Thiazolo[3,2-c]1,2,4-triazin-5-ones

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HETEROANNULATION THROUGH PALLADIUM CATALYSIS: A NOVEL CYCLIZATION LEADING TO REGIOSELECTIVE SYNTHESIS OF 3-SUBSTITUTED THIAZOLO[3,2-C]1,2,4-TRIAZIN-5-ONES

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A convenient, general, and one-pot synthesis of substituted thiazolo-[2,3-c]1,2,4-triazinone from 3-propargylmercapto-1,2,4-triazin-5-one and aromatic iodide via palladium catalysis is described.

Keywords: Aryl halides; one-pot synthesis; palladium catalysis; regioselective cyclization; thiazolotriazine

INTRODUCTION

The bicyclic compounds derived from 1,2,4-triazine have both fundamental and applied interest. Its synthesis defies conventional heterocyclization strategies and isomeric systems have proven pharmacological value.[1–3] Many efforts have been devoted to the preparation of the thiazolo-1,2,4-triazines using catalyzed intermolecular functionalization of an acetylenic moiety.[4–8] However, regioselective synthesis of related substituted thiazolo-1,2,4-triazines in a one pot reaction have been largely overlooked.

There has been considerable interest of late in transition metal-mediated cycloaddition reactions of aldehydes in organic synthesis,[9] especially those involving palladium.[10,11] Attempts to annulate

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intramolecularly onto alkynes using palladium have generally resulted in multiple alkyne insertion and subsequent cyclization back to the preexisting aromatic ring.[12] Although a few multistep procedures[13] are available for the synthesis of carbocyclic[14] and heterocyclic compounds,[15] using palladium, this annulation strategy has not been utilized for the synthesis of thiazolotriazines.

In continuation of our recent studies[1,6,16,17] on the palladium-catalyzed reactions of acetylenic substrates leading to heterocyclic compounds of biological significance, we became interested in the regioselective synthesis of substituted thiazolotriazines using palladium-copper catalysis.

RESULTS AND DISCUSSION

When 3-propargylmercapto-1,2,4-triazin-5-ones **2** was treated with aryl halides **3a–e** in triethylamine in the presence of bis(triphenylphosphin) palladium chloride and copper iodide, 3-substituted thiazolo[2,3-c]-triazin-5-ones were obtained in good to high yields.

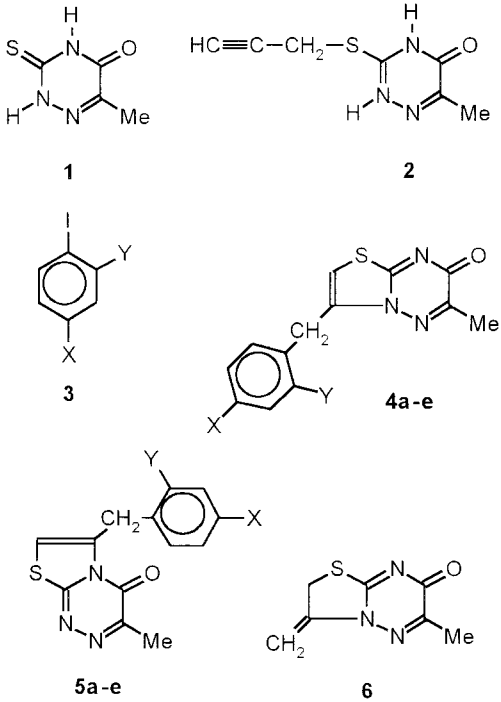
In general, we have used a strategy similar to those used by us for earlier annulation reactions.[5–8,16,17] In the first step, 6-methyl-1,2,4-triazine-3(2H)thione-5(4H)-one **1** was reacted with propargyl bromide to give the corresponding 3-propargylmercapto derivative **2**.[18] Heteroannulation of **2** through palladium-copper catalysis in the presence of aryl iodides led to either substituted thiazolo[3,2-b]1,2,4-triazines **4** or thiazolo[2,3-c]1,2,4-triazines **5**.

The reactions were usually carried out by stirring a mixture of aryl iodides **3a–e** and mercapto acetylenic compounds **2** in the presence of the palladium catalyst, copper(I) iodide and a base in acetonitrile (CH_3CN). The results are shown in Table I. As can be seen in most cases the thiazolotriazines were obtained in high yields.

Bis(triphenylphosphine) palladium chloride and triethylamine were found to be the catalyst and base of choice respectively. However

TABLE I M.P. and Yield of the Prepared Compounds **5a–5c**

	ArI				
Entry	X	Y	m.p. (°C)	Cryst. solvent	Yield (%)
a	NO_2	H	237–235	Me_2CO	80
b	NO_2	Cl	234–235	MeOH	87
c	H	NO_2	232–234	MeOH	72
d	CN	H	238–239	EtOH	78
e	Cl	CN	229–230	EtOH	83



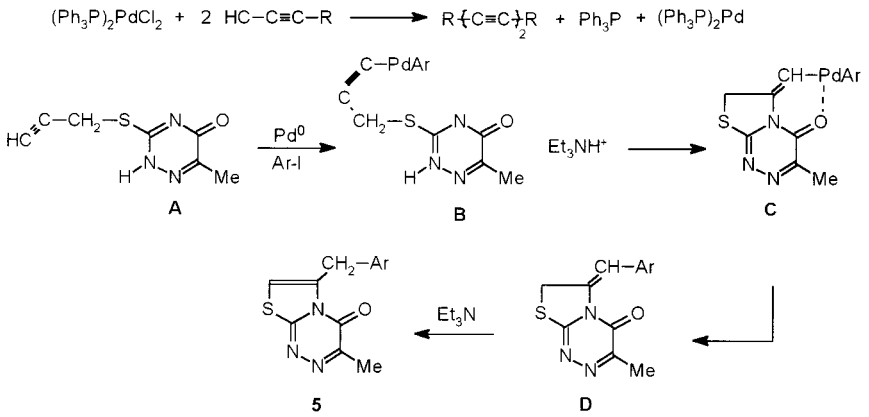
cuprous iodide was found to be an essential cocatalyst. Reactions carried out either with copper(I) iodide or Pd(II)-catalyst alone led to very poor yields of product mixtures.

The presence of electron withdrawing groups such as $-NO_2$, Cl^-, —CN on aryl halides seems to be essential. When PhI was used as an aryl halide only a small amount of product could be separated by coloumn chromatoghraphy. The main product of this reaction was 3-methylene-6-methyl, 2,3-dihydro triazolo[3,2-b]1,2,4-triazino-7-one **6**. Compound **6** has been synthesized via base catalyzed heterocyclization of **2**.[4]

The structures of **4** or **5** were established by comparison of their spectra with those of well-established **7** (λ_{max} 280 nm),[18] **8** (λ_{max} 282 nm),[16,17] and **9** (λ_{max} 298 nm).[5]

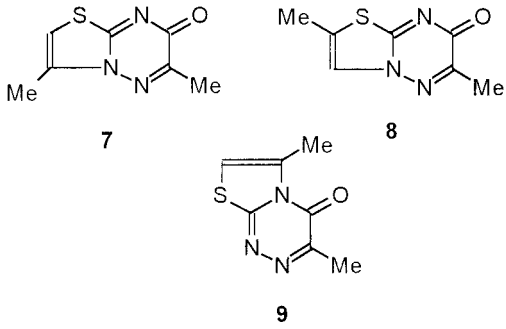
3,4-Disubstituted-1,2,4-triazin-5-ones are known to show, the absorption maxima at longer wavelength compared to 2,3-disubstituted compounds.[19] The UV spectrum of **4** or **5** was quite similar to that of **9**. Therefore, we concluded that one-pot condensation, cyclization, and isomerization of acetylenic compounds has regioselectively afforded **5**.

Mechanistically, the formation of thiazolo[2,3-c]1,2,4-triazine could be explained as shown in Scheme 1. The alkynyl palladium species



SCHEME 1

3 could undergo cyclization either around N2 or N4 of 1,2,4-triazine. Coordination between oxygen and palladium in **C** ensure the cyclization with N4 and lead to triazolo[2,3-c]1,2,4-triazines **5**.



In conclusion we have established the first successful one-pot condensation, regioselective cyclization, and isomerization for the synthesis of thiazolo[2,3-c]1,2,4-triazine. The method is easy to carry out under relatively mild condition. Since there is no need to any toxic reagents, it can be considered relatively, eco-friendly. The process is thus amenable to the regioselective synthesis of thiazolo[2,3-c]1,2,4-triazines.

EXPERIMENTAL

The melting points are uncorrected and were obtained by a Kolfer Heizbank Rechart type 7841, melting point apparatus. IR spectra were obtained on a 4300 Schimadzu spectrometer. The ^{1}HNMR spectra were recorded on a Brucker AC100 unless otherwise stated using TMS as

internal reference and mass spectra on a Varian CH-7 instrument at 70 eV. Microanalyses were performed by the Institute of Petroleum Industry of Iran.

Synthesis of 3-Substituted 5H-Thiazolo[3,2-c]1,2,4-triazin-5-one, 5a

Typical Reaction Condition

A mixture of aryl iodide (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.025 mmol), CuI (0.055 mmol), and triethylamine (0.27 mmol) was stirred in acetonitrile (6 mL) under an argon atmosphere. The acetylenic compound (1.275 mmol) was then added and the mixture stirred at room temperature for 12 h. The solid was filtered, washed with water, and crystallized from a suitable solvent (Table I).

Selected data for **5a**, ^{1}HNMR, δ(d_6-DMSO), 2.5 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 7.1 (s, 1H, CH of thiazole ring), 7.6 (d, 2H, C_6H_4), 8.2 (d, 2H, C_6H_4), IR, $\tilde{\upsilon}$ (KBr disc): 3100, 1638, 1525, 1350 cm^{-1}; MS, M^+, m/e 302(5), 300(10), 299(45), 257(100), 100(22); UV ($CHCl_3$), λ_{max} 298 nm; elemental analysis $C_{13}H_{10}N_4O_3S$ (302.31 g/mol), calcd. C 51.65; H, 3.33; N, 18.54%, found C 51.79; H 3.39; N 18.56%.

Selected data for **5b**, ^{1}HNMR, δ(d_6-DMSO), 2.23 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.03 (s, 1H, CH of thiazole ring), 7.65 (d, 2H, C_6H_4), 8.15 (d, 2H, C_6H_4), 8.34 (s, 1H, C_6H_4). IR, $\tilde{\upsilon}$ (KBr disc): 3100, 1640, 1520, 1475, 800, 735 cm^{-1}; MS, M^+, m/e 327 (M^{2+}, 30), 295(8), 293(21), 255(100), 210(88), 70(40); UV ($CHCl_3$), λ_{max} 300 nm; elemental analysis $C_{13}H_9N_4O_3SCl$ (336.75 g/mol), calcd. C 46.36; H, 2.69; N, 16.64%, found C 46.52; H 2.70; N 16.69%.

Selected data for **5c**, ^{1}HNMR, δ(d_6-DMSO), 2.21 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 6.93 (s, 1H, CH of thiazole ring), 7.5–7.73 (d, 3H, C_6H_4), 8.05 (d, 2H, C_6H_4), IR, $\tilde{\upsilon}$ (KBr disc): 3100, 1640, 1520, 1480, 1440, 790 cm^{-1}; MS, M^+, m/e 302(75), 301(93), 239(97), 238(100), 224(97), 150(74); UV ($CHCl_3$), λ_{max} 302 nm; elemental analysis $C_{13}H_{10}N_4O_3S$ (302.31 g/mol), calcd. C 51.65; H, 3.33; N, 18.54%, found C 51.73; H 3.38; N 18.57%.

Selected data for **5d**, ^{1}HNMR, δ(d_6-DMSO), 2.23 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 7.01 (s, 1H, CH of thiazole ring), 7.53 (d, 2H, C_6H_4), 7.81 (d, 2H, C_6H_4), IR, $\tilde{\upsilon}$ (KBr disc): 3080, 1635, 1380, 1250, 820 cm^{-1}; MS, M^+, m/e 282(7), 279(37), 235(100), 234(49), 137(40), 84(56); UV ($CHCl_3$), λ_{max} 295 nm; elemental analysis $C_{14}H_{10}N_4OS$ (282.32 g/mol), calcd. C 55.30; H, 3.57; N, 19.85, found C 55.41; H 3.59; N 19.90.

Selected data for **5e**, ^{1}HNMR, δ(d_6-DMSO), 2.23 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 7.10 (s, 1H, CH of thiazole ring), 7.52 (d, 2H, C_6H_4), 7.73 (d, 1H, C_6H_4), 8.06 (s, 1H, C_6H_4), IR, $\tilde{\upsilon}$ (KBr disc): 3170, 2220, 1640, 1480, 1380 cm^{-1}, MS, M^+, m/e 317 (M^{2+}, 8.7), 315 (M^+, 8),

275(37), 272(100), 84(43); UV ($CHCl_3$), λ_{max} 305 nm; elemental analysis $C_{14}H_9N_4OSCl$ (316.77 g/mol), calcd. C 49.29; H, 2.86 N, 17.69%, found C 49.35; H 3.87; N 17.71%.

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