Synthesis of Thiazolo[3,2-*d*][1,2,4] Triazines through Palladium-catalyzed Heteroannulation of acetylenic Compounds

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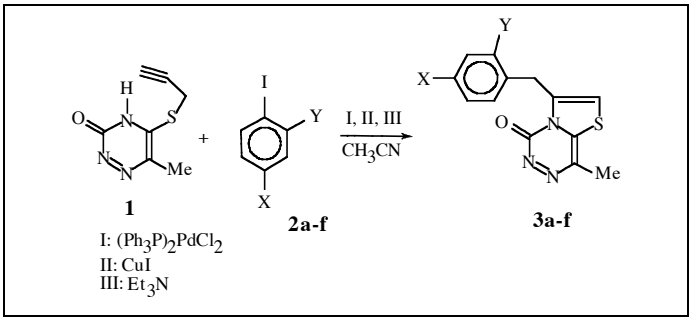

The reaction of 6-methyl-5-(prop-2-ynylthio)-5,6-dihydro-1,2,4-triazin-3(4*H*)-one **1** with various iodobenzenes **2** in the presence of palladium catalyst leads to the formation of substituted triazolotriazines.

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INTRODUCTION

The bicyclic compounds from 1,2,4-triazine have both fundamental and applied interest. Its synthesis needs conventional heterocyclization strategies and isomeric systems have proven pharmacological value [1-2]. The chemistry of thiazolotriazine has been well documented [3].

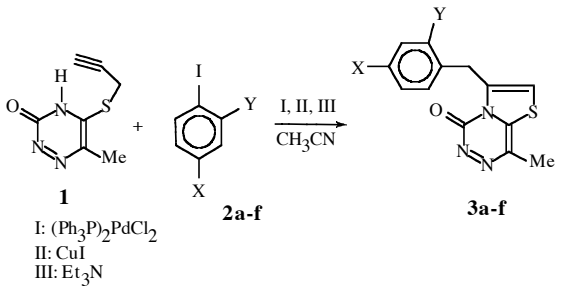
There has been considerable interest in transition metal mediated cycloaddition reaction of alkynes in organic synthesis [4] especially those involving palladium [5]. Palladium catalyzed cyclization reactions of 3-(prop-2-ynylthio)1,2,4-triazines to thiazolo-1,2,4-triazinones have reported by Mizutani *et al*. [6]. We have used this strategy for the synthesis of a novel heterocyclic system, thiazolo[3,2-*d*][1,2,4] triazine [7]. In continuation of our studies [7] on the palladium catalyzed reactions of acetylenic substrates, we are interested in developing a general synthesis of thiazolo[3,2-*d*][1,2,4] triazines using palladium-copper catalysis [8].

RESULTS AND DISCUSSION

In this communication we wish to report that when 6-methyl-5-(prop-2-ynylthio)-5,6-dihydro-1,2,4-triazin-3(4*H*)-one (**1**) [7] is treated with an aryl halide in triethylamine in the presence of bis(triphenylphosphine)palladium (**II**) chloride and coprous iodide, 3-benzyl substituted thiazolo[3,2-*d*]-1,2,4-triazinones are obtained in high yields (Scheme 1, Table 1).

Although bis(triphenylphosphine) palladium(II) chloride is the catalyst of choice, it seems however that copper(I) iodide is an essential co-catalyst. Reactions carried out with $[(PPh_3)_2PdCl_2]$ alone led to very poor yields of product mixture. When copper(I) iodide was used alone no reaction took place. Triethyl amine was found to be the base of choice. Use of this base gives cleaner products and better yields.

Scheme 1



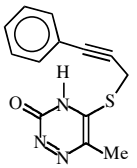
The reaction was carried out by stirring a mixture of acetylenic compound **1** and aryl iodide **2a-f** in the presence of palladium catalyst, copper(I) iodide and triethylamine in acetonitrile. The results are shown in table 1.

Table 1

Reaction of **1** with **2a-f** Catalyzed by Pd

Entry	ArI		Mp (°C)	Yield (%)
	X	Y		
3a	NO_2	H	232	82
3b	NO_2	Cl	224	95
3c	H	NO_2	227	84
3d	CN	H	230	78
3e	Cl	CN	222	87
3f	H	H	181	43

When iodo benzene was used as an aryl halide (**2**; X, Y=H), in the same reaction condition, the condensed product **4** was isolated. The subsequent reflux in a mixture of triethylamine in DMF gave **3f** (X, Y=H, Scheme 1).



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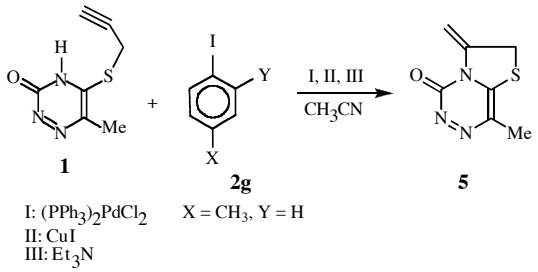
It is worthwhile to mention that when *p*-iodotoluene (X=CH_3, Y=H, **2g**) was used as an aryl iodide, the cyclization occurred without the participation of aryl iodide to afford 8-methyl-3-methylene-2,3-dihydro-5*H*-[1,3]-thiazolo[3,2-*d*][1,2,4]triazin-5-one (**5**) (Scheme **2**). This compound has been already synthesized and reported [7].

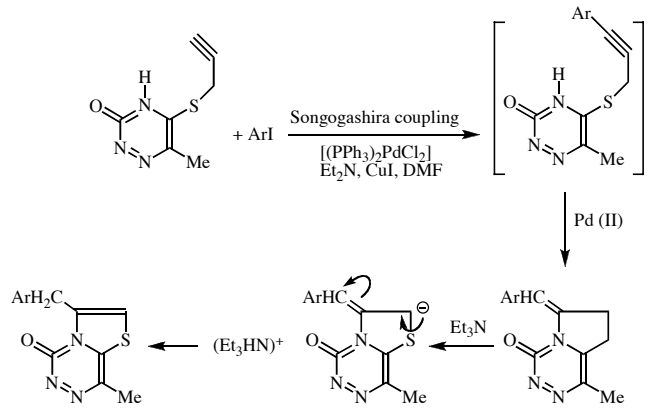
Scheme 2



Mechanistically, the formation of 3-benzyl substituted thiazolo[3,2-*d*][1,2,4]triazin-5-one could be explained as shown in Scheme 3.

This thiazolotriazine synthesis presumably proceeds *via* oxidative addition of the mercaptoalkyne into aryl palladium bond nitrogen displacement of the palladium in the resulting phenylpalladium intermediate quite possibly *via* a six membered intermediate palladacycle and subsequent reductive elemination. The last step obviously involves the isomerization and aromatization catalyzed by triethylamine. To make sure that the reaction is Pd catalyzed this reaction was coducted only with catalytic amounts of CuI. In this case very small amounts of product was detected on tlc along with large amounts of starting materials.

Scheme 3



In conclusion, we have developed a successful palladium catalyzed reaction for the synthesis 3-aryl substituted thiazolo[3,2-*d*]triazinone from readily available starting materials. This method is carried out under mild condition free from any toxic reagent.

EXPERIMENTAL

Melting points are uncorrected and were obtained by a Kofler Heizbank Reichart type 7841 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}HNMR spectra were recorded on a Bruker AC 100, unless otherwise stated using TMS as standard reference. Mass spectra scanned on a Varian CH-7 instrument at 70 eV.

Synthesis of 8-methyl-3-substituted-5*H*-[1,3]thiazolo[3,2-*d*]-[1,2,4]triazine-ones (3). A typical reaction condition. A mixture of aryl iodide **2a**-**f** (0.75 mmol), [$(PPh_3)_2PdCl_2$] (0.0175 g, 0.025 mmol) and triethylamine (0.2 mL, 0.275 mmol) was stirred in acetonitrile (6 mL) under argon atmosphere for 3 min at ambient temperature. 6-Methyl-5-(prop-2-ynylthio)-5,6-dihydro-1,2,4-triazin-3(4*H*)-one **1** (0.231 g, 1.275 mmol) was then added and the reaction mixture was then stirred for 12 hrs at room temperature. The solid was collected by filtration, washed with water and crystallized from ethanol to afford the product **3a-f** (Table 1).

8-Methyl-3(4-nitrobenzyl)-5*H*-[1,3]thiazolo[3,2-*d*][1,2,4]-triazin-5-one (3a). This compound was obtained as a creamy powder in 82% yield., mp 232 °C, ^{1}HNMR, δ($CDCl_3$), 2.42 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 6.46 (s, 1H, CH), 7.5 (d, 2H, J= 8Hz), 8.25 (d, 2H, J= 8Hz), IR, ν(KBr disc): 3060, 1632, 1482, 1374 cm^{-1}; MS, M$^+$, m/e 302(7), 300(10), 299(52), 251(100), 211(80), 188(92), 180(60), 157(70), 143(89), 113(43), 101(87). *Anal.* Calcd. for $C_{13}H_{10}N_4SO_3$ (302.13) calcd.: C, 51.64; H, 3.33; N, 18.53%. Found: C, 51.68; H, 3.29; N, 18.49%.

3-(2-Chloro-4-nitrobenzyl)-8-methyl-5*H*-[1,3]thiazolo[3,2-*d*]-[1,2,4]triazin-5-one (3b). This compound was obtained as a creamy powder in 95% yield, mp 224°C, ^{1}HNMR, δ(d_6-DMSO), 2.23 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 7.03 (s, 1H, CH), 7.65 (d, 1H, J= 8.5Hz), 8.10-8.2 (dd, 1H, J_1= 8.5Hz, J_2= 2Hz), 8.32 (d, 1H, J= 2Hz); IR, ν(KBr disc): 3068, 1633, 1475, 1345, 897 cm^{-1}; MS, M$^+$, m/e 337(5), 335(12), 334(16), 257(100), 209(30), 84(53). *Anal.* Calcd. for $C_{13}H_9ClN_4SO_3$ (336.75) calcd.: C, 46.36; H, 2.69; N, 16.63%. Found: C, 46.19; H, 2.60; N, 16.51%.

8-Methyl-3-(2-nitrobenzyl)-5*H*-[1,3]thiazolo[3,2-*d*][1,2,4]-triazin-5-one (3c). This compound was obtained as a creamy powder in 84% yield, mp 227 °C, ^{1}HNMR, δ(d_6-DMSO), 2.36 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 6.69 (s, 1H, CH), 7.47-7.77 (m, 3H, ArH), 8.05 (d, 1H, J= 7Hz); IR, ν(KBr disc): 3075, 1637, 1482, 1338, 792 cm^{-1}; MS, M$^+$, m/e 302(11), 301(49), 298(68), 237(84), 225(40), 222(66), 181(33), 155(48), 84(90), 44(100),

28(98. *Anal.* Calcd. for $C_{13}H_{10}N_4SO_3$ (302.13) calcd.: C, 51.64; H, 3.33; N, 18.53%. Found: C, 51.68; H, 3.29; N, 18.49%.

3-[4-Cyanobenzyl]-8-methyl-5*H*-[1,3]thiazolo[3,2-*d*][1,2,4]-triazin-5-one (3d). This compound was obtained as a creamy powder in 78% yield.mp 230 °C,^{1}HNMR, δ($CDCl_3$), 2.41 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 6.40 (s, 1H, CH), 7.42 (d, 2H, J= 8Hz), 7.68 (d, 2H, J= 8Hz), IR, ν(KBr disc): 3072, 2230, 1630, 1471 cm^{-1}; MS, M^+, m/e 282(10), 280(19), 237(92), 234(96), 207(42), 171(98), 167(99), 127(100). *Anal.* Calcd. for $C_{14}H_{10}N_4SO$ (282.32) calcd.: C, 59.56; H, 3.57; N, 19.84%. Found: C, 60.00; H, 3.53; N, 19.90%.

3-[4-Chloro-2-cyanobenzyl]-8-methyl-thiazolo[3,2-*d*][1,2,4]-triazin-5-one (3e). This compound was obtained as a creamy powder in 87% yield, mp 222 °C,^{1}HNMR, δ(d_6-DMSO), 2. 23 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 7.1 (s, 1H, CH), 7.53 (d, 1H, J= 8Hz), 7.67(dd, 1H, J_1= 8Hz, J_2= 2.5Hz), 8.07 (s, 1H, J= 2.5Hz), IR, ν(KBr disc): 3049, 2226, 1630, 1482, 876 cm^{-1}; MS, M+2, m/e 315(60), 313(94), 263(98), 234(51), 212(60), 148(98), 103(66), 83(98), 67(100). *Anal.* Calcd. for $C_{14}H_9N_4SO$ (316.74) calcd.: C, 53.08; H, 2.86; N, 17.68%. Found: C, 53.00; H, 2.90; N, 17.59%.

3-(Benzyl)-8-methyl-5*H*-[1,3]thiazolo[3,2-*d*][1,2,4]triazin-5-one (3f). This compound was obtained as a creamy powder in 43% yield.mp 181-183 °C, ^{1}HNMR, δ($CDCl_3$), 2.43 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 6.24 (s, 1H, CH), 7.26-7.35 (m, 5H, ArH); IR, ν(KBr disc): 3100, 1646, 1487, 1373, 1260 cm^{-1}; MS, M^+, m/e 257(9), 254(51), 215(78), 181(82), 165(100), 127(50), 86(49); elemental analyses for $C_{13}H_{11}N_3SO$ (257.31) calcd.: C, 60.68; H, 4.30; N, 16.33%. Found: C, 60.59; H, 4.25; N, 16.29%.

6-Methyl-5[(3-phenyl-2-propynyl)sulfanyl]-1,2,4-triazin-3(4*H*)-one(4). To a solution of sodium methoxide(0.02 mol), 6-methyl[1,2,4]triazine-3- one-5- thione (0.01 mol) in methanole (50ml), propargyl bromide (.015 mol) was gradually added on stirring which was continued for 4 hours at room temperature. The volume reduced to half under vacuo and acetic acid(2ml) was added. The residue was filtered off and recrystalized from ethanole as creamy powder. Mp 181°C; yield 58%; ^{1}HNMR, δ(d_6-DMSO), 2.13 (s, 3H, CH_3), 4.27 (s, 2H, CH_2), 7.38 (s, 5H, ArH), 13.83 (s broad, 1H, NH), IR, ν(KBr disc): 3675, 3089, 1635, 1476, 1347 cm^{-1}; MS, M^+, m/z 257(30), 254(41), 213(43), 201(57), 85(100), 76(62). *Anal.* Calcd. for $C_{13}H_{11}N_3SO$ (257.31) calcd.: C, 60.68; H, 4.30; N, 16.33%. Found: C, 60.59; H, 4.25; N, 16.29%.

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