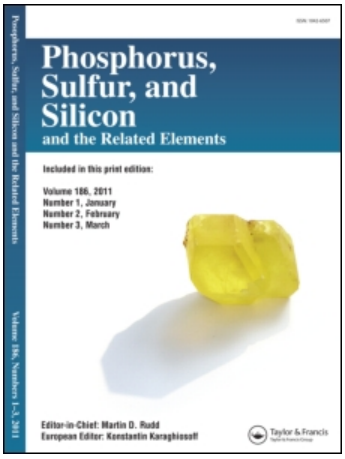

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Regioselective Synthesis of 3-Benzylthiazolo[3,2-a]pyrimidones and 3-Benzyl-thiazolo[3,2-c]pyrimidones Through Palladium-Catalyzed Heteroannulation of Acetylenic Compounds

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*The reaction of 2-(prop-2-ynylsulfanyl)pyrimidone **1** with various iodobenzenes in the presence of a palladium catalyst leads to regioselective cyclization to 3-benzylthiazolo [3,2-a] pyrimidones **3**. The reaction of 4-(prop-2-ynylsulfanyl) pyrimidone **5** with various iodobenzenes in the same condition give the corresponding 3-benzylthiazolo[3,2-c]pyrimidones **6**.*

Keywords Acetylenic compounds; palladium-catalyzed heteroannulation; regioselective cyclization; thiazolopyrimidines

INTRODUCTION

Up until now, the general method for synthesizing thiazolo[3,2-a] pyrimidines has been basically dependent on starting from

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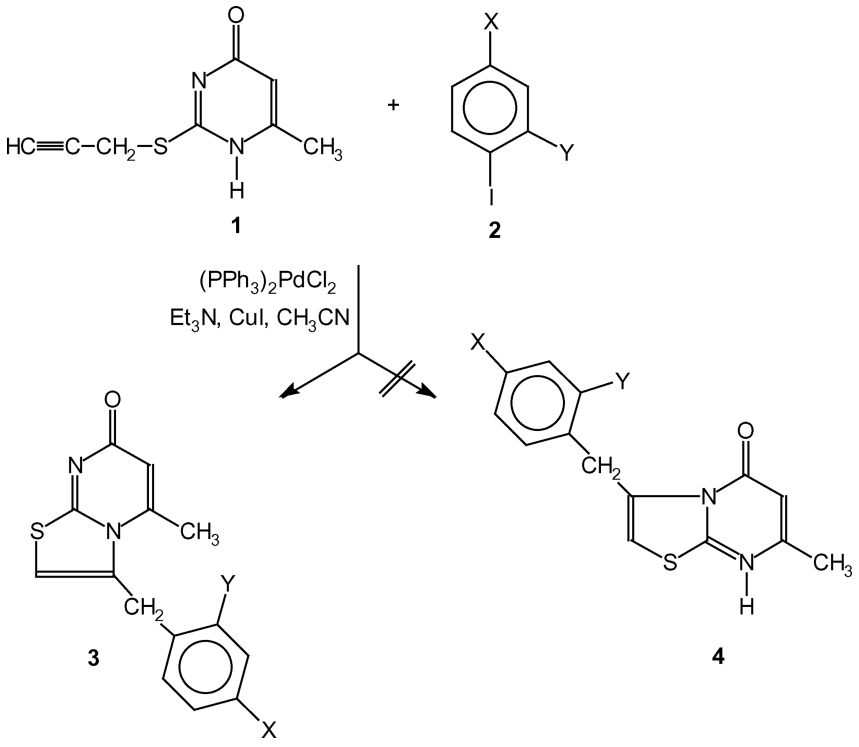
2-aminothiazoles.[1] Many thiazolo[3,2-a] pyrimidines have been synthesized to evaluate their biological activities.[2] However, these synthetic methods have the disadvantages of giving another regioisomer, thiazolo [2,3-b] pyrimidines. Although palladium-catalyzed cyclization reactions of 2-propynylsulfanylpyrimidones has been reported to give thiazolo[3,2-a]pyrimidone,[3] all attempts made so far to reach pure regioisomeric thiazolo [3,2-a] pyrimidone have invariably led to failure or poor yields [1–3]. Moreover none of these methods led to the synthesis of substituted thiazolo [3,2-a] pyrimidones.

Palladium-catalyzed annulation strategies have been successfully utilized for the synthesis of carboxylic[4] and heterocyclic compounds.[5] As we studied[6] palladium-catalyzed reactions of acetylenic substrates leading to heterocyclic compounds of biological significance, we became interested in developing a regioselective synthesis of substituted thiazolopyrimidines.



SCHEME 1

In this communication, we wish to report that when 6-methyl-2(prop-2-ynylsulfanyl) pyrimidone-4-one **1** was treated with 4-nitro-1-iodobenzene **2a** in triethylamine in the presence of bis(triphenylphosphine) palladium chloride and copper iodide, 5-methyl-3-(4-nitrobenzyl)-1H-thiazolo[3,2-a] pyrimidon-7-one **3** was obtained in good yield. It means that carbometalation/anion capture, cyclization, and aromatization have occurred in a one-pot reaction.

From spectral data, the elucidation of the structure was quite straightforward. ^{1}HNMR showed one aromatic proton at δ 6.6, which was characteristic of a fused thiazole ring as well as benzylic protons at δ 4.6. The mass spectrum showed M^+ at m/z 301. The spectral data, however, were not much help in deciding in favor of either product **3** or product **4** (Scheme 1).

The product, however, was crystallized as colorless needles that was suitable for X-ray diffraction and was identified as 3-(p-nitrobenzyl)-5-methyl-7H-thiazolo [3,2-a] pyrimidon-7-one **3**. The molecules crystallize in the triclinic space group P-1 with two molecules in the unit cell. Table I contains a summary of data collection conditions and results. Selected bond distances and angles are listed in Table II. Most of the bond

TABLE I Crystallographic Data for 3

Formula	$C_{14}H_{11}N_3O_3S$	ρ_{calc} (g/cm^3)	1.573
Formula mass (g/mol)	301.32	Temperature (K)	193
Crystal size (mm)	0.23 × 0.09 × 0.04	μ (cm^{-1})	2.7
a (pm)	673.9(1)	$2\theta_{max}$ (°)	51.84
b (pm)	853.2(1)	H	$-8 \rightarrow 8$
c (pm)	1109.6(2)	K	$-10 \rightarrow 10$
α(°)	88.30(2)	L	$-13 \rightarrow 13$
β(°)	86.84(2)	Measured reflections	5295
γ(°)	87.81(2)	Unique reflections	2309
V (pm^3.10^6)	636.3(2)	Data with $F_o > 4\sigma(F_o)$	1202
Space group	P-1	Parameter	192
Z	2	R_1 [$F_o > 4\sigma(F_o)$]	0.037
		wR_2 (all data)	0.067[a]
Used programs	SIR-92,[7]	Max./min. residual	0.19/ −0.22
	SHELXL-97,[8]	Electron density	
	SHELXTL,[9]	(e/pm^3·10^6)	
	PLATON-98[10]		

[a] $w = 1/[\sigma^2(F_o) + (0.0152 \cdot P)^2]$; $P = \{\text{Max}(F_o^2, 0) + 2 \cdot F_c^2\}/3$.

Crystallographic data (excluding structure factors) for the crystal structure has been deposited at the Cambridge Crystallographic Data Center with the number CCDC-197303. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. E-mail: deposite@ccdc.cam.ac.uk

TABLE II Selected Bond Distances (pm) and Bond Angles (°) of 3

S1-C1	172.0(3)	N2-C1	138.6(3)
S1-C7	172.5(3)	N2-C4	140.8(3)
O1-C2	122.9(3)	N2-C6	143.0(3)
O2-N3	122.3(3)	N3-C84	147.1(4)
O3-N3	123.5(3)	C6-C7	132.5(3)
N1-C1	131.0(3)	C6-C8	149.8(4)
N1-C2	138.7(3)		
C1-S1-C7	90.1(1)	C4-N2-C6	131.2(2)
S1-C7-C6	114.7(2)	C7-C6-C8	124.2(2)
C1-N1-C2	117.7(2)	C6-C8-C81	111.5(2)
C1-N2-C4	116.4(2)	C84-N3-O2	118.2(3)
C1-N2-C6	112.3(2)	C84-N3-O3	117.9(3)

distances and angles are in the range observed in similar compounds. The dihedral angle between the planes containing the fused [6,5] heterocyclic ring system and the nitrobenzene ring (C7-C6-C8-C81) is 89° (Figure 1).

The reactions were usually carried out by mixing acetylenic compound **1** with aryliodides **2** in the presence of palladium catalyst, copper(I) iodide, and triethylamine in acetonitrile. The results are shown in Table III. The yields were found to be good to high. Bis(triphenylphosphine) palladium chloride was found to be the catalyst of choice. The heteroannulation process is regioselective and leads to thiazolo [3,2-a] pyrimidones. To establish the generality of the method, various iodobenzenes were reacted with **1** in the same conditions to afford the corresponding thiazolo[3,2-a]pyrimidones **3** (Table III).

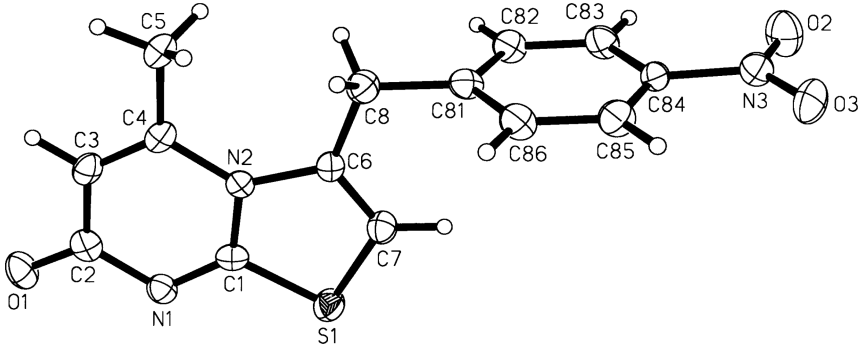
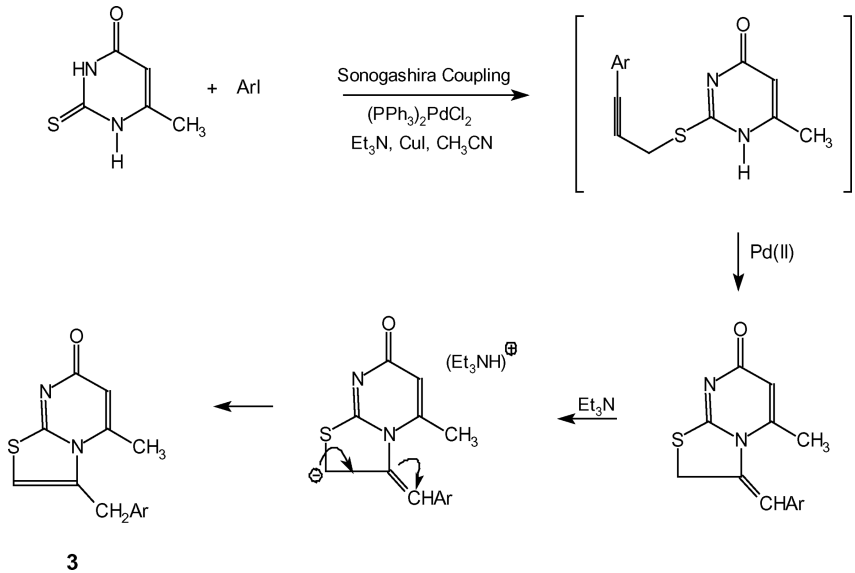


FIGURE 1 Graphic representation of **3**, (ellipsoids 50% with H-atoms).

TABLE III Palladium-Catalyzed Heteroannulation of Acetylenic Compounds 1 Leading to Thiazolo[3,2-a] Pyrimidones 3

	ArX				
Entry	X	Y	Recryst. solvent	Mp (°C)	Yield (%)
3a	NO_2	H	Ethylacetate	265	82
3b	NO_2	Cl	Ethanol	248	75
3c	H	NO_2	Methanol	229	80
3d	CN	H	Ethanol	236	85
3e	Cl	H	Ethanol	298	78

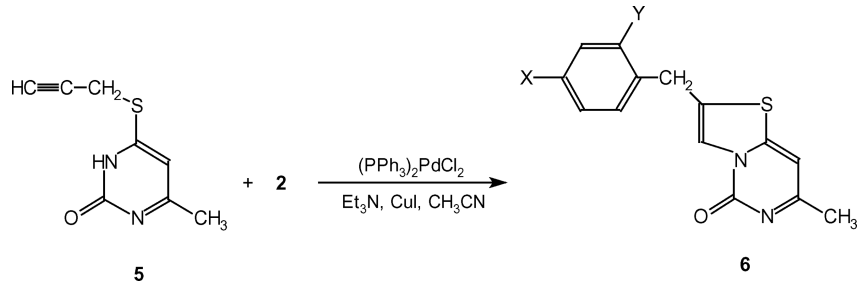


3

SCHEME 2

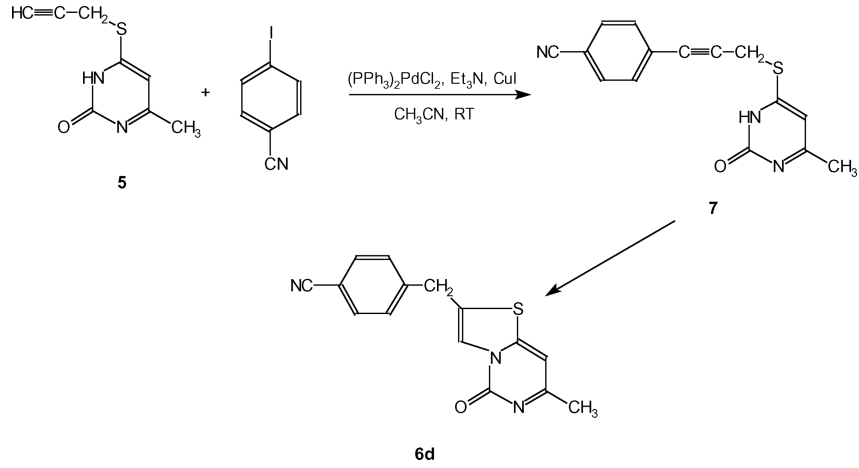
The mechanism of the reaction is illustrated in Scheme 2. Most probably, a two step process occurs: first, a standard Sonoghashira coupling[11] and known Pd(II) catalyzed intermolecular cyclization of the nucleophilic nitrogen moiety onto the triple bond, and, base-induced aromatization. We have recently reported this kind of one-pot heterocyclization for the synthesis of 3-benzylthiazolo-[3,2-a] benzimidazole.[12]

Under a similar condition, the reaction of 4-(prop-2-ynylsulfanyl) pyrimidone **5**[6c] with various iodobenzenes in the presence of a palladium catalyst leads to cyclization to 3-benzyl-thiazolo[3,2-c] pyrimidones **6** (Table IV).



5 6

SCHEME 3



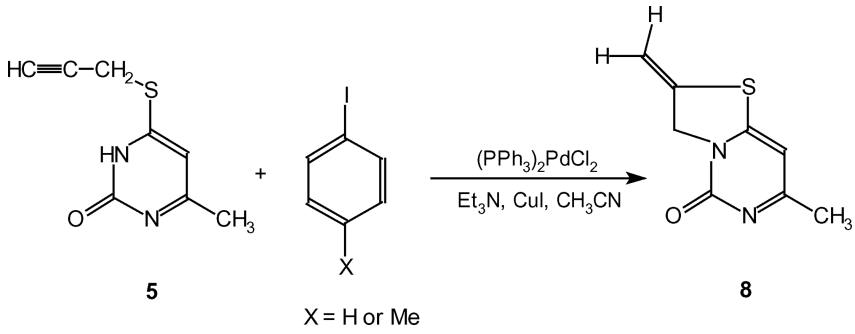
5 7 6d

SCHEME 4

It is worthwhile mentioning that in the case of using p-iodobenzenonitrile as an aryl iodide, the condensed product **7** can be isolated at room temperature. The latter can be subsequently cyclized by refluxing in a mixture of Et_3N, EtOH to the corresponding thiazolo[3,2-c]pyrimidone **6e** (Table IV).

It also is noteworthy that in the case of using iodobenzene or *p*-iodotoluene as an aryl iodide, the cyclization occurs without involvement of the aryl iodide. The product of such a reaction was identified to be 2,3-dihydro-3-methylene-7-methyl-thiazolo[3,2-c]pyrimidon-5-one **8** (Scheme 5).

Compound **8** already has been synthesized through the catalytic cyclization of **5** with $PdCl_2(PhCN)_2$.[6c]



SCHEME 5

EXPERIMENTAL

The ^{1}HNMR spectra were recorded on a Bruker AC 100 and the chemical shifts were determined using TMS as the internal standard. The IR spectra were obtained on a Shimatzu spectrometer. The mass spectra were recorded on a Varian 7 CH mass spectrometer. Melting points were determined by the capilary method on an electrically heated melting point apparatus (Kofler Reichert type 7841).

REACTION OF ACETYLENIC COMPOUND 1 WITH ARYL IODIDES. A GENERAL PROCEDURE

A mixture of aryl iodide (1.5 mmole), 0.035 g [$(PPh_3)_2PdCl_2$] (0.05 mmole), 0.021 g CuI (0.11 mmol), and 0.4 mL triethylamine (2.9 mmole) in acetonitrile (12 mL) was stirred under nitrogen for 20 min. The acetylenic compound **1** (2.55 mmole, 0.459 g) was then added and stirred at room temperature for 1 h. The solid was filtered, washed with water, and crystallized from suitable solvent to afford the corresponding thiazolo[3,2-a]pyrimidones (Table III).

TABLE IV Palladium-Catalyzed Heteroannulation of Acetylenic Compounds 5 Leading to Thiazolo[3,2-c] Pyrimidones 6

	ArX				
Entry	X	Y	Recryst. solvent	Mp °C	Yield %
6a	NO_2	H	EtOH	244–245	87
6b	NO_2	Cl	EtOH	223–224	89
6c	H	NO_2	EtOH	189–190	83
6d	Cl	CN	EtOH	202–203	70
6e	CN	H	EtOH	221–222	93

Selected Spectroscopic Data for 3a

^{1}HNMR, δ(d_6-DMSO) 2.53 (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 6.07(s, 1H, CH), 6.66(s, 1H, CH), 7.53(d, $J = 8.4$, 2H, ArH), 8.26(d, $J = 8.4$, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 3100, 1635, 1520, 1480, 1345, 870, 742 cm^{-1}, MS m/z 301(10) M^+, 299(20), 298(100), 283(11), 281(28), 271(13).

Selected Spectroscopic Data for 3b

^{1}HNMR, δ(d_6-DMSO) 2.52 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.07(s, 1H, CH), 6.65(s, 1H, CH), 7.55(d, $J = 8.4$, 1H, ArH), 8.21(d, $J = 8.4$, 2H, ArH), 8.38(d, $J = 8.4$, 1H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 3100, 1640, 1600, 1480, 1350, 860, 790 cm^{-1}, MS m/z 337(3.5) M^{+2}, 332(30), 330(100), 298(17), 296(83), 267(10), 254(16), 248(10).

Selected Spectroscopic Data for 3c

^{1}HNMR, δ(d_6-DMSO) 2.53 (s, 3H, CH_3), 4.69 (s, 2H, CH_2), 6.07(s, 1H, CH), 6.51(s, 1H, CH), 7.43(d, $J = 7.4$, 2H, ArH), 7.62–7.78(m, 2H, ArH), 8.15(d, $J = 7.4$, 1H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 3100, 1635, 1520, 1480, 1350, 858, 745 cm^{-1}, MS m/z 301(10) M^+, 300(27), 299(100), 282(34), 250(19), 191(44), 176(45), 138(48).

Selected Spectroscopic Data for 3d

^{1}HNMR, δ(d_6-DMSO) 2.51 (s, 3H, CH_3), 4.51 (s, 2H, CH_2), 6.04(s, 1H, CH), 6.57(s, 1H, CH), 7.43(d, $J = 7.9$, 2H, ArH), 7.86(d, $J = 7.9$, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 2240, 1635, 1590, 1485, 1400 cm^{-1}, MS m/z 281(5) M^+, 280(17), 276(100), 278(59), 250(32), 168(39), 137(53), 112(27).

Selected Spectroscopic Data for 3e

^{1}HNMR, δ(d_6-DMSO) 2.56 (s, 3H, CH_3), 4.59 (s, 2H, CH_2), 6.08(s, 1H, CH), 6.57(s, 1H, CH), 7.43(d, $J = 7.9$, 2H, ArH), 7.80(d, $J = 7.9$, 1H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 3100, 2240, 1630, 1485, 1400, 868 cm^{-1}, MS m/z 317(13) M^{+2}, 315(41) M^+, 313(100), 284(13), 224(26), 170(16), 150(11), 137(10).

REACTION OF ACETYLENIC COMPOUND 5 WITH ARYL IODIDES: A GENERAL PROCEDURE

A mixture of aryl iodide (0.75 mmol), 0.0175 g bis (triphenylphosphin) palladium(II) chloride (0.025 mmole), 0.011 g copper(I) iodide (0.055

mmole) and 0.2 mL triethylamine (1.4 mmole) in acetonitrile (8 mL) was stirred under dry argon for 20 min. The acetylenic compound **5** (1.275 mmol, 0.231 g) was then added and stirred at ambient temperature for 2 h. The solid was filtered, washed with water, and crystallized from EtOH to afford **6a** and **6b** (Table IV). In the case of **6c** and **6d**, the above solid was first column chromatographed using $CHCl_3$ as an eluent. The products were crystallized for further purification from EtOH (Table IV).

Selected Spectroscopic Data for 6a

^{1}HNMR, δ(d_6-DMSO) 2.22 (s, 3H, CH_3), 4.70 (s, 2H, CH_2), 7.00(s, 1H, CH), 7.23(s, 1H, CH), 7.47(d, $J = 8.7$, 2H, ArH), 8.16(d, $J = 8.7$, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 1666 1497, 1347, 894 cm^{-1}, MS m/z 301(14) M^+, 299(62), 243(18), 188(12), 144(45), 123(50), 99(40), 74(35), 45(56), 29(100).

Selected Spectroscopic Data for 6b

^{1}HNMR, δ(d_6-DMSO) 2.24 (s, 3H, CH_3), 4.74(s, 2H, CH_2), 7.04(s, 1H, CH), 7.12(s, 1H, CH), 7.32(d, $J = 7.0$, 2H, ArH), 8.05–8.34(m, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 1679, 1568, 1516, 1352, 898 cm^{-1}.

Selected Spectroscopic Data for 6c

^{1}HNMR, δ(d_6-DMSO) 2.22(s, 3H, CH_3), 4.83(s, 2H, CH_2), 6.99(s, 1H, CH), 7.06(s, 1H, CH), 7.26(d, 2H, ArH), 7.49–7.65 (m, 2H, ArH), 8.03(d, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 1666 1416, 1356 cm^{-1}, MS m/z 301(8) M^+, 299(14), 281(18), 237(20), 123(60), 106(75), 89(70), 75(46), 52(42), 44(100).

Selected Spectroscopic Data for 6d

^{1}HNMR, δ(d_6-DMSO) 2.23(s, 3H, CH_3), 4.74 (s, 2H, CH_2), 7.01(s, 1H, CH), 7.12(s, 1H, CH), 7.23(d, 2H, ArH), 7.62–8.03(m, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 2226, 1677, 1557, 1484, 1388 cm^{-1}, MS m/z 317(3) M + 2, 315(8) M^+, 311(10), 267(39), 174(100), 78(25), 69(90), 44(20), 38(45).

REACTION OF 5 WITH P-IODOBENZONITRILE. SYNTHESIS OF 6-METHYL-4[3-(4-CYANO-PHENYL)-2(PROPSULFONYL) PYRIMIDIN-2-ONE 7

A mixture of 0.17 g *p*-iodobenzonitrile (0.75 mmole), 0.0175 g $(PPh_3)_2PdCl_2$ (0.025 mmole), 0.01 g CuI (0.05 mmol), and 0.2 mL

triethylamine (1.4 mmole) in acetonitrile (8 mL) was stirred under dry argon for 20 min. The acetylenic compound **5** (1.275 mmole, 0.231 g) was added and this mixture was stirred for 2 h. The solid was filtered off, washed with water, and crystallized from EtOH to afford **7**. Yield 75%, m.p. 204–205 °C (EtOH), ^{1}HNMR, δ(d_6-DMSO) 2.14(s, 3H, CH_3), 4.27 (s, 2H, CH_2), 6.26(s, 1H, CH), 7.58(d, 2H, ArH), 7.83(d, 2H, ArH), 11.62(s broad, 1H, NH). IR $\tilde{\upsilon}$ (KBr disc) 3737, 2226, 1667, 1268, 1104 cm^{-1}, MS m/z 281(6) M^+, 280(13), 279(39), 278(96), 232(21), 170(81), 137(100), 123(58), 106(78), 66(70), 53(49), 44(97), 38(53).

Cyclization of 7 to 6e

Compound **7** (0.498 mmol, 0.15 g) was refluxed in a mixture of 0.2 mL triethylamine (0.275 mmole) and ethanol (5 mL) for 1 h. The reaction mixture was cooled to room temperature. The solid was filtered off and recrystallized from EtOH to afford 6a (Table IV). Yield 93%, m.p. 221–222°C (EtOH), ^{1}HNMR, δ(d_6-DMSO) 2.22(s, 3H, CH_3), 4.64 (s, 2H, CH_2), 7.00(s, 1H, CH), 7.17(s, 1H, CH), 7.40(d, 2H, ArH), 7.77(d, 2H, ArH). IR $\tilde{\upsilon}$ (KBr disc) 2221, 1689, 1502, 1381, 894 cm^{-1}, MS m/z 281(7) M^+, 280(18), 279(43), 278(100), 233(23), 167(55), 137(66), 114(50), 76(50), 66(68).

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