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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1607–1610

Regioselective synthesis of 6-benzylthiazolo-[3,2-*b*]1,2,4-triazoles during Sonogashira coupling

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Received 29 September 2004; revised 9 January 2005; accepted 19 January 2005
Available online 1 February 2005

Abstract—The reaction of 3-mercaptopropargyl-1,2,4-triazoles with various iodobenzenes catalyzed by Pd–Cu leads to the regioselective formation of 6-benzylthiazolo[3,2-*b*]1,2,4-triazoles **4**. The structure of **4d** was confirmed by X-ray analysis.

1. Introduction

The azole antifungals appear to offer scope for providing truly effective drugs.[1] Imidazole antifungals such as clotrimazole, miconazole and ketoconazole show good activity, but are only of limited value for systemic administration.[2] Triazole derivatives possess a broad spectrum of antifungal activity and reduced toxicity compared with the imidazole antifungals.[2]

Although several methods have been reported for the synthesis of thiazolo[3,2-*b*]1,2,4-triazoles,[3] those which use 3-mercapto-1,2,4-triazoles **1** as the starting materials have the disadvantage of also giving regioisomeric thiazolo[2,3-*c*]1,2,4-triazoles.[4]

Pd-catalyzed annulation has been utilized successfully for the synthesis of carboxylic[5] and heterocyclic compounds.[6] In continuation of our recent studies[7] on Pd-catalyzed reactions of acetylenes leading to heterocyclic compounds of biological significance, we became interested in developing a regioselective synthesis of substituted thiazolo-1,2,4-triazoles.

3-Mercapto-1,2,4-triazoles **1** (R = CH_3 and Ph)[8] were reacted with propargyl bromide in refluxing ethanol to yield the corresponding 3-propargylmercapto-1,2,4-triazoles **2**.[8] When **2** (R = Ph) was treated with 4-nitro-1-iodobenzene **3d** and triethylamine in the presence of bis(triphenylphosphine)palladium chloride and copper iodide, a single compound was obtained as detected by TLC. The ^{1}H NMR spectrum of the product showed one aromatic proton at δ 6.52 ppm, characteristic of a fused thiazole ring, as well as benzylic protons at δ 6.52 ppm. The mass spectrum showed an M^+ at *m/z* 336.

Mechanistically, either thiazolo-1,2,4-triazines **4d** or **5d** were possible products as illustrated in Scheme 1. Probably a two-step process had occured: a standard Sonogashira coupling[9] followed by a Pd(II)-catalyzed intermolecular cyclization of either nitrogen 2 or nitrogen 4 onto the triple bond followed by base-induced aromatization.[10]

However, other mechanisms for this reaction are also plausible, for example, cyclization via initial generation of the exocyclic olefin followed by an intermolecular Heck reaction, which would provide a facile pathway for migration of the double bond into the endocyclic position[11] or alternatively a 5-*exo* dig. cyclization may be simply triggered by the formation an Ar–Pd(II) species followed by reduction, elimination–isomerization. This type of cyclization has been observed for acetylenic lactams.[12]

Keywords: Sonogashira coupling; Thiazoles; Triazoles; Pd-catalyzed reaction; Thiazolotriazoles.
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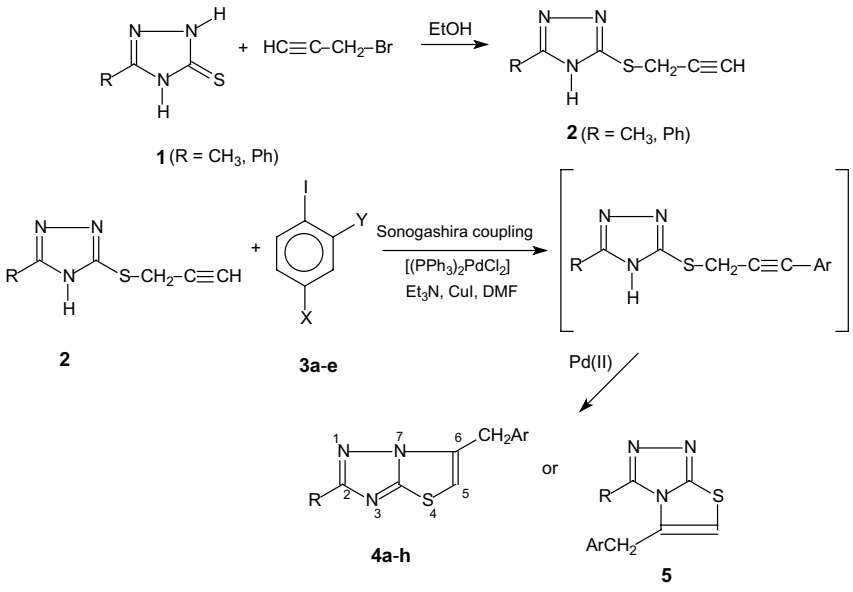
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.091



Scheme 1.

The spectral data were not much helpful in deciding in favor of either product **4d** or **5d**. The product, however, crystallized as colorless needles suitable for X-ray crystallography and was identified as 6-(4-nitrobenzyl)-2-phenylthiazolo[3,2-*b*]1,2,4-triazole **4d**. The molecule crystallized in the triclinic space group *P*-1 with four molecules in the unit cell. The crystallographic data of **4d** are listed in Table 1 and the selected bond lengths and bond angles are given in Table 2. Figure 1 shows a perspective view of the structure of **4d**. The thiazolo[3,2-*b*]1,2,4-triazole ring system is planar and has a geometry similar to that reported for another compound with a similar ring system.[3b]

Table 1. Crystallographic data for **4d**

Formula	$C_{17}H_{12}N_4O_2S$	ρ_{calc} (g/cm^3)	1.499
Formula mass (g/mol)	336.37	Temperature (K)	193
Crystal size (mm)	$0.52 \times 0.4 \times 0.14$	μ (cm^{-1})	2.4
a (pm)	751.5(1)	$2\theta_{max}$ (°)	52.62
b (pm)	1076.2(1)	*h*	$-9 \rightarrow 9$
c (pm)	1093.0(1)	*k*	$-13 \rightarrow 13$
α (°)	61.23(1)	*l*	$-13 \rightarrow 13$
β (°)	87.11(1)	Measured reflections	10,844
γ (°)	74.92(1)	Unique reflections	2993
V (pm^{3}10^6)	745.3(1)	Data with $F_o > 4\sigma(F_o)$	2602
Space group	*P*-1	Parameter	265
Z	4	$R_1[F_o > 4\sigma(F_o)]$	0.0488
		wR_2 (all data)	0.1342[a]
Programs used	SHELXS-97[13]	Max residual	0.58
	SHELXL[14]	Electron density (e/pm$^3 \times 10^6$)	
	ORTEP[15]		
	PLATON-98[16]		

Crystallographic data (excluding structure factors) for the crystal structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC-257521. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax.: int. code +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk).

[a] $w = 1/[\sigma^2(F_o) + (0.01047 \times P)^2 + (0.02P)]$; $P = \{\mathrm{Max}(F_o^2, 0) + 2 \times F_c^2\}/3$.

The dihedral angles between the 'best planes' of the compound are 72° for A and B (A: S1 N1 N2 N3 C1 C2 C3 C4 and B: C32 C33 C34 C35 C36 C37) and 3° for A and D (D: C41 C42 C43 C44 C45 C46) and 2° for B and C (C: N4 O1 O2).

To establish the generality of the synthesis, several aryl iodides **3a**–**e** were reacted with **2** (R = CH_3 and Ph) by this method to afford compounds **4a**–**h** in good to high yields (Table 3). The presence of electron-withdrawing groups such as –NO_2, –Cl and –CN on the aryl iodide seems to be essential. When PhI was used as the aryl halide, a complicated mixture was obtained.

The reactions must be carried out under an argon atmosphere and the mixture of DMF and triethylamine must be degassed prior to use. Bis(triphenylphosphine) palladium chloride and triethylamine were found to be the catalyst and base of choice.

Copper iodide was found to be an essential cocatalyst. Reactions carried out just with either copper(I) iodide

Table 2. Selected bond lengths (pm) and bond angles (°) of **4d**

S1–C1	172.2(2)	N3–C4	137.2(2)
S1–C2	174.5(2)	N3–C1	131.9(2)
C2–C3	134.5(2)	C3–C31	149.4(2)
N1–C1	135.2(2)	C4–C41	147.1(2)
N1–C3	139.6(2)	C35–N4	146.5(2)
N1–N2	136.1(2)	N4–O1	122.6(2)
C4–N2	133.7(2)	N4–O2	122.6(2)
C1–S1–C2	89.67(8)	C4–N3–C1	101.5(1)
S1–C2–C3	114.0(1)	N3–C1–S1	138.2(1)
C2–C3–N1	109.5(1)	N3–C1–N1	111.2(2)
C3–N1–N2	116.4(2)	N1–C3–C31	120.0(2)
N1–N2–C4	101.1(1)	C3–C31–C32	112.1(2)
N2–C4–N3	116.1(2)	C35–N4–O2	118.2(1)

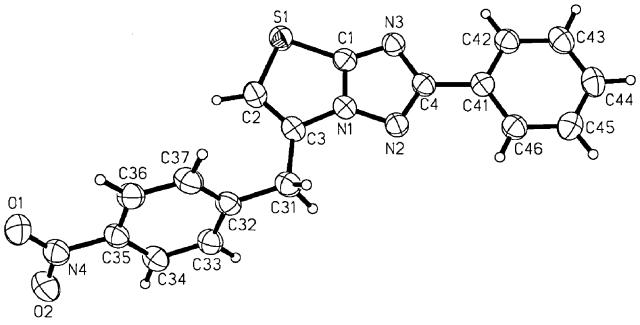


Figure 1. Perspective view of the crystal structure of **4d** (thermal ellipsoids at 50% probability).

Table 3. Melting points and yields of the prepared 6-benzylthiazolo[3,2-*b*]1,2,4-triazoles

Product	1,2,4-Triazole R	ArI		Mp (°C)	Yield[a] (%)
		X	Y		
4a	CH_3	NO_2	H	128–129	57
4b	CH_3	CN	H	112–114	54
4c	CH_3	H	NO_2	116–117	48
4d	Ph	NO_2	H	168	81
4e	Ph	NO_2	Cl	165–166	65
4f	Ph	H	NO_2	184	78
4g	Ph	Cl	CN	126–127	62
4h	Ph	CN	H	156	68

[a] Yields refer to isolated products.

or Pd(II) chloride as the catalyst led to very poor yields of products.

In summary, we have developed an efficient and extremely useful method for the regioselective synthesis of 6-substituted benzylthiazolo[3,2-*b*]1,2,4-triazoles.

2. Experimental

2.1. General procedure for the preparation of 6-substituted thiazolo[3,2-*b*]1,2,4-triazoles

A mixture of the aryl iodide (0.75 mmol), $(PPh_3)_2PdCl_2$ (0.025 mmol), CuI (0.055 mmol) and triethylamine (2 mmol) was stirred in DMF (5 mL) in a round-bottomed flask under an argon atmosphere at ambient temperature. The appropriate 3-propargyl mercapto-1,2,4-triazole (**2**, R = CH_3, Ph) was then added and the mixture was stirred at room temperature for 24 h. Upon completion of the reaction, water (5 mL) was added and the mixture was extracted with $CHCl_3$. The chloroform layer was separated and concentrated and the crude product was subjected to column chromatography using $CHCl_3$–MeOH, 98/2% as eluent to afford the product (Table 3).

2.2. Selected data for 4a

Yield: 57%, mp: 128–129 °C, ^{1}H NMR, δ ($CDCl_3$) 2.53 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 6.50 (s, 1H, CH of thiazole), 7.52 (d, J = 7.8 Hz, 2H, ArH), 8.22 (d, J = 8.6, 2H, ArH). IR ν (KBr disc) 1517, 1344 cm^{-1}, MS *m*/*z* 274. Anal. Calcd for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.42. Found: C, 51.98; H, 3.64; N, 20.50.

2.3. Selected data for 4b

Yield: 54%, mp: 112–114 °C, ^{1}H NMR, δ ($CDCl_3$) 2.53 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 6.45 (s, 1H, CH of thiazole), 7.46 (d, J = 8.0 Hz, 2H, ArH), 7.66 (d, J = 8.1, 2H, ArH). IR ν (KBr disc) 2269 cm^{-1}, MS *m*/*z* 254. Anal. Calcd for $C_{13}H_{10}N_4S$: C, 61.39; H, 3.96; N, 22.03. Found: C, 61.42; H, 3.86; N, 21.99.

2.4. Selected data for 4c

Yield: 48%, mp: 116–117 °C, ^{1}H NMR, δ ($CDCl_3$) 2.52 (s, 3H, CH_3), 4.57 (s, 2H, CH_2), 6.49 (s, 1H, CH of thiazole), 7.46–7.60 (m, 3H, ArH), 8.05 (d, J = 8.3, 1H, ArH). IR ν (KBr disc) 1520, 1350 cm^{-1}, MS *m*/*z* 274. Anal. Calcd for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.42. Found: C, 52.14; H, 3.58; N, 20.70.

2.5. Selected data for 4d

Yield: 81%, mp: 168 °C, ^{1}H NMR, δ ($CDCl_3$) 4.36 (s, 2H, CH_2), 6.52 (s, 1H, CH of thiazole), 7.42–7.61 (m, 5H, ArH), 8.11–8.26 (m, 4H, ArH). IR ν (KBr disc) 1516, 1347 cm^{-1}, MS *m*/*z* 336, UV ($CDCl_3$) λ_{max} 264.4 nm. Anal. Calcd for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.59; N, 16.65. Found: C, 60.57; H, 3.47; N, 16.49.

2.6. Selected data for 4e

Yield: 65%, mp: 165–166 °C, ^{1}H NMR, δ ($CDCl_3$) 4.48 (s, 2H, CH_2), 6.62 (s, 1H, CH of thiazole), 7.42–7.48 (m, 3H, ArH), 7.72 (d, J = 8.1 Hz, 1H, ArH), 8.06–8.31 (m, 4H, ArH). IR ν (KBr disc) 1518, 1352 cm^{-1}, MS *m*/*z* 370, UV ($CHCl_3$) λ_{max} 263.2 nm. Anal. Calcd for $C_{17}H_{11}ClN_4O_2S$: C, 55.06; H, 2.98; N, 15.10. Found: C, 55.00;H, 3.01; N, 15.02.

2.7. Selected data for 4f

Yield: 78%, mp: 184 °C, ^{1}H NMR, δ ($CDCl_3$) 4.67 (s, 2H, CH_2), 6.62 (s, 1H, CH of thiazole), 7.44–7.67 (m, 6H, ArH), 7.14–8.19 (m, 3H, ArH). IR ν (KBr disc) 1515, 1345 cm^{-1}, MS *m*/*z* 336, UV ($CHCl_3$) λ_{max} 261 nm. Anal. Calcd for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.59; N, 16.65. Found: C, 60.65; H, 3.53; N, 16.55.

2.8. Selected data for 4g

Yield: 62%, mp.: 126–127 °C, ^{1}H NMR, δ ($CDCl_3$) 4.45 (s, 2H, CH_2), 6.78 (s, 1H, CH of thiazole), 7.26–7.73 (m, 6H, ArH), 8.11–8.21 (m, 2H, ArH). IR ν (KBr disc) 2226 cm^{-1}, MS *m*/*z* 350 (M^+), UV ($CHCl_3$) λ_{max} 258.4 nm. Anal. Calcd for $C_{18}H_{11}ClN_4S$: C, 61.62; H, 3.16; N, 15.96. Found: C, 61.55; H, 3.14; N, 16.00.

2.9. Selected data for 4h

Yield: 68%, mp: 156 °C, ^{1}H NMR, δ (d_6-DMSO) 4.35 (s, 2H, CH_2), 7.02 (s, 1H, CH of thiazole), 7.37–7.64 (m, 6H, ArH), 8.01–8.10 (m, 3H, ArH). IR ν (KBr disc)

2221 cm^{-1}, MS *m/z* 316, UV ($CHCl_3$) λ_{max} 285 nm. Anal. Calcd for $C_{18}H_{12}N_4S$: C, 68.33; H, 3.82; N, 17.70. Found: C, 68.00; H, 3.79; N, 16.98.

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