Chinese Chemical Letters 27 (2016) 37–40

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

C–H Arylation using acyl thiourea ligands: Applications in the synthesis of 3,6-diaryl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles

Aamer Saeed *, Pervaiz Ali Channar, Qasir Iqbal, Jamaluddin Mahar

Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

ARTICLE INFO

Article history:
Received 17 June 2015
Received in revised form 5 August 2015
Accepted 19 August 2015
Available online 25 September 2015

Keywords:
[1,2,4]Triazolo[3,4-b] [1,3,4]thiadiazoles
Acyl thiourea
C–H arylative coupling
N,N-Dimethylacetamide

ABSTRACT

Synthesis of a series of new 3,6-diaryl-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazoles (**5a**–**o**) was achieved by phophine free, C–H arylative cross-coupling of 6-aryl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**4a**–**o**) with suitably substituted iodoanilines using 1-(2-naphthoyl)-3-(4-bromophenyl)thiourea as a ligand. The requisite triazolothiadiazoles (**4a**–**o**) were obtained by the condensation of 4-amino-1,2,4-triazole-3-thiol (**3**) with suitably substituted aromatic acids in the presence of phosphoryl chloride.

1. Introduction

Carbon–carbon coupling reactions are among the most powerful synthetic tools used in the synthesis of complex molecules such as natural products. Mizoroki and Heck independently reported the first carbon–carbon bond-forming reaction that followed a Pd(0)/Pd(II) catalytic cycle. It involved the coupling of aryl or vinyl halides and activated alkenes in the presence of a base [1,2]. Conversely, there has long been an increasing interest in the transition metal-catalyzed functionalization of relatively unactivated carbon-hydrogen (C–H) bonds for the new C–C, C–O, or C–S bond formation. This approach is straightforward, environmentally friendly and avoids the use of protective/leaving groups, thus significantly shortening the synthetic routes [3,4]. The C–H activation finds applications in the synthesis of natural products, functional materials, and pharmaceuticals. Some recent examples include the palladium-catalyzed enantioselective C–H arylation in the synthesis of P-stereogenic compounds [5], palladium(II)-catalyzed directed trifluoromethylthiolation of unactivated C(sp^3)–H bonds [10], cobalt catalyzed low temperature CH alkenylations with alkenyl acetates, phosphates, carbonates or carbamates [6] and photocatalytic CH activation by hydrogen-atom transfer [7]. Moreover, direct C–H amination for indole synthesis from N-Ts-2-styrylaniline derivatives catalyzed by copper salt [8], multi-substituted arenes *via* palladium catalyzed C–H halogenation [9], efficient synthesis of 2-arylquinazolines *via* copper-catalyzed dual oxidative benzylic C–H aminations of methylarenes [10] have also been reported.

Thiourea derivatives have long been employed as organocatalysts for various organic transformations. These ligands have also been used in palladium catalyzed Heck and Suzuki–Miyaura cross coupling reactions [11,12]. *N,N′*-Monosubstituted acyclic thiourea and 1-aroyl-3-arylthiourea ligands have been utilized as highly active phosphine-free catalysts for palladium catalyzed Heck reactions of aryl iodides or bromides with styrenes and acrylates. The 1-aroyl-3-arylthiourea ligands giving best results included the simple 1-benzoyl-3-phenylthiourea and 1-(4-bromobenzoyl)-3-(4-bromophenyl)thiourea with bulky bromo-substituents [13].

Substituted triazolo[3,4-b][1,3,4]thiadiazoles are the key structural motifs of numerous compounds with activity relevant to biological and medicinal chemistry [14,15]. Therefore, there is an unrelenting strong requirement for developing new strategies for the synthesis of these heterocycles.

The significance and utilization of the theories mentioned above together with the availability of our library of diverse 1-acyl-3-arylthiourea derivatives [16], encouraged us to explore the C–H activated coupling of 6-aryl [1,2,4]triazolo [3,4-b][1,3,4]thiadiazole with different aryl iodides in the presence of 1-(2-naphthoyl)-3-(4-bromophenyl)thiourea.

2. Experimental

Melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected. ^{1}H

* Corresponding author.
E-mail addresses: asaeed@qau.edu.pk, aamersaeed@yahoo.com (A. Saeed).

http://dx.doi.org/10.1016/j.cclet.2015.09.011

NMR and ^{13}C NMR spectra were determined at 300 MHz and 75 MHz, respectively, using a Bruker AM-300 spectrophotometer. FTIR spectra were recorded on a Bio-Rad-Excalibur Series Mode FTS 3000 MX spectrophotometer. Mass Spectra (EI, 70 eV) on a GC-MS, Agilent Technologies 6890N and an inert mass selective detector 5973 mass spectrometer Technologies and elemental analyses were conducted using a LECO-183 CHNS analyzer. Thin layer chromatography (TLC) was conducted on 0.25 mm silica gel plates (60 F254, Merck).

2.1. Synthesis of 6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**4a**–**o**)

4-Amino-4*H*-1,2,4-triazole-3-thiole (1 equiv.) (**3**) was taken in a two-necked round bottom flask equipped with magnetic stirrer and suitable benzoic acid (1 equiv.) was added followed by the dropwise addition of the $POCl_3$ (10 mL). The reaction mixture was refluxed at 180 °C for 10 h. On completion, the reaction mixture was cooled and neutralized with $NaHCO_3$ and the solids obtained were filtered and recrystallized from water and ethanol (8:2) to afford products (**4a**–**o**) in 69%–81% yields.

2.2. Synthesis of 3-aryl-6-phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**5a**–**o**)

$Pd(OAc)_2$ (5 mol%) and thiourea ligand (3 mol%) were added to 15 mL of DMA (15 mL) and stirred well under argon. Then, CaO (1.5 equiv.) followed by that of corresponding triazolo-thiadiazole (**4a**–**o**) (1.0 equiv.) were added to the reaction mixture and refluxed at 140 °C for 1 h. After cooling to room temperature 4-iodoaniline derivative (1.0 equiv.) was added and the mixture refluxed for 15–20 h. The reaction progress was monitored by TLC analysis using a solvent system (methanol:chloroform = 0.5:9.5) or (ethyl acetate: *n*-hexane = 6:4). On completion, the reaction mixture was poured into 50 mL of water. The water layer was extracted twice with 25 mL of DCM, dried (anhydrous sodium sulphate) filtered and concentrated. The products were purified by recrystallization or by column extraction using *n*-hexane/ethyl acetate (3:1) to yield the 3,6-diphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**5a**–**o**).

3,6-Diphenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5a**): Yellow solid, R_f = 0.67 (petroleum ether:ethyl acetate = 7:3); IR (KBr, cm^{-1}): 1605 (N=O str), 1514 (C=N str), 1494 (Ar, C=C str), 1185 (Ar, C–C str), 990 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 7.52–7.45 (m, 5H, *J* = 9.0 Hz, Ar-H), 7.39–7.42 (m, 5H, *J* = 9.0 Hz, Ar-H), ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 167.04, 141.9, 133.3 (C=N), 131.9, 131.9, 130.4, 130.05, 129.9, 129.7, 128.6, 127.8 (ArCs), Anal. Calcd. for $C_{15}H_{10}N_4S$: C, 64.73; H, 3.62; N, 20.13; S, 11.52; found: C, 64.71; H, 3.64; N, 20.13; S, 11.52. GC-MS *m*/*z*: 278.0 (M^+, 100).

6-Phenyl-3-*m*-tolyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5b**): Yellow solid, R_f = 0.66 (petroleum ether:ethyl acetate = 7:3); IR (KBr, cm^{-1}): 2921 (Ar, C–H str), 2851 (methyl, C–H str), 1602 (nitro N=O str), 1510 (C=N str), 1492 (Ar, C=C str), 1185 (Ar C–F str), 990 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 7.70 (d, 1H, *J* = 1.2 Hz), 7.68–7.54 (m, 1H, Ar-H), 7.42–7.30 (m, 2H, Ar-H), 7.39–7.42 (m, 5H, *J* = 9 Hz, Ar-H), 2.42 (s, 3H, $ArCH_3$). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 167.04, 141.9, 133.3 (C=N), 131.9, 131.9, 130.4, 130.05, 129.9, 129.7, 128.6, 127.8 (ArCs), 21.58 (CH_3), Anal. Calcd. for $C_{16}H_{14}N_4S$: C, 65.73; H, 4.14; N, 19.17; S, 10.96; found: C, 65.71; H, 4.16; N, 19.15; S, 10.98. EI-MS *m*/*z*: 292.0 (M^+, 100).

6-Phenyl-3-*p*-tolyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5c**): Yellow solid; R_f = 0.68 (petroleum ether:ethyl acetate = 7:3); IR (KBr, cm^{-1}): 3064 (Ar, C–H str), 2923 (methyl, C–H str), 1517 (C=N str), 1466 (Ar, C=C str), 971 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 8.28 (d, 2H, *J* = 7.5 Hz, Ar-H), 8.10 (d, 1H, *J* = 7.5 Hz, Ar-H) 7.90–7.24 (m, 5H, *J* = 9 Hz, Ar-H), 2.41 (s, 3H, $ArCH_3$). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 167.0, 140.9, 133.0 (C=N), 132.9, 131.7, 130.1, 130.0, 129.8, 129.6, 128.5, 127.7 (ArCs), 21.55 (CH_3), Anal. Calcd. for $C_{16}H_{14}N_4S$: C, 65.73; H, 4.14; N, 19.16; S, 10.97; found: C, 65.71; H, 4.16; N, 19.15; S, 10.98. EI-MS *m*/*z*: 292.0 (M^+, 100).

3-(4-Chlorophenyl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5d**): Light yellow solid; R_f = 0.66 (petroleum ether:ethyl acetate = 7:3) IR (KBr, cm^{-1}): 2921 (Ar, C–H str), 2851 (methyl, C–H str), 1602 (nitro N=O str), 1510 (C=N str), 1492 (Ar, C=C str), 1185 (Ar C–F str), 990 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 7.73 (d, 2H, *J* = 7.8 Hz, ArH), 7.47 (d, 2H, *J* = 7.8 Hz, ArH), 7.39–7.42 (m, 5H, *J* = 9 Hz, Ar-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 165.2, 151.0, 146.3 (C=N), 143.9, 131.9, 129.5, 128.3, 127.8, 124.6, 123.5, 114.5 (ArCs). Anal. Calcd. for $C_{1s}H_9ClN_4S$: C, 57.60; H, 2.90; N, 17.91; S, 10.25; found: C, 57.62; H, 2.88; N, 17.90; S, 10.26. EI-MS *m*/*z*: 312.0, 314.0 (M^+, 100).

3-(4-Nitrophenyl)-6-phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5e**): Yellow solid; R_f = 0.56 (petroleum ether:ethyl acetate = 7:3); IR (KBr, cm^{-1}): 2921 (Ar, C–H str), 2851 (methyl, C–H str), 1602 (nitro N=O str), 1510 (C=N str), 1492 (Ar, C=C str), 1185 (Ar C–F str), 990 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 7.36 (d, 2H, *J* = 8.1 Hz, Ar-H), 8.36 (d, 2H, *J* = 8.4 Hz, Ar-H); 7.39–7.42 (m, 5H, *J* = 9 Hz, Ar-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 166.2, 153.0, 146.4 (C=N), 145.9, 132.9, 129.6, 127.3, 126.8, 126.6, 124.5, 115.5 (ArCs); Anal. Calcd. for $C_{1s}H_9N_5O_2S$: C, 55.72; H, 2.81; N, 21.66, S, 9.92; found: C, 55.70; H, 2.83; N, 21.65; S, 9.93. EI-MS *m*/*z*: 323 (M^+, 100).

4-(6-Phenyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)benzenamine (**5f**): Light brown; R_f = 0.62 (petroleum ether:ethyl acetate = 7:3); IR (KBr, cm^{-1}): 3064 (Ar, C–H str), 2923 (methyl, C–H str), 1518 (C=N str), 1465 (Ar, C=C str), 971 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 8.03 (d, 2H, *J* = 8.0 Hz, ArH), 7.96 (d, 2H, *J* = 7.5 Hz, ArH), 7.66–6.72 (m, 5H, *J* = 9 Hz, Ar-H), 5.69 (s, 2H, NH_2). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 165.7, 152.4, 150.8 (C=N), 146.3, 132.7, 129.5, 129.0, 127.1, 129.1, 113.6, 112.3 (ArCs). Anal. Calcd. for $C_{1s}H_{11}N_5S$: C, 61.42; H, 3.78; N, 23.87; S, 10.93; found: C, 61.40; H, 3.80; N, 23.86; S, 10.94. EI-MS *m*/*z*: 293 (M^+, 100).

6-Phenyl-3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5g**): Yellow solid; R_f = 0.66 (petroleum ether:ethyl acetate 7:3); IR (KBr, cm^{-1}): 3080 (sp^2 CH), 1626 (C=N), 1505 (C=C), 1266 (N–N=C triazolo-thiadiazole), 669 (C-S-C), ^1H NMR (DMSO-d_6): δ 8.84–8.25 (m, 4H, Py), 8.10–7.65 (m, 5H, *J* = 9 Hz; Ar-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 167.5 150.7, 143.7, (C=N), 133.1 132.4, 129.7, 128.8, 127.4, 126.4, 126.3, 119.4, (ArCs). Anal. Calcd. for $C_{14}H_9N_5S$, C, 60.20; H, 3.25; N, 25.07; S, 11.48; found: C, 60.22; H, 3.86; N, 25.09; S, 11.46. EI-MS *m*/*z*: 279 (M^+, 100).

3-(4-Chlorophenyl)-6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5h**): Yellow solid; R_f = 0.33 (petroleum ether:ethyl acetate 7:3); IR (KBr, cm^1): 2921 (Ar C–H str), 2851 (methyl C–H str), 1602 (nitro N=O str), 1510 (C=N str), 1492 (Ar, C=C str), 1185 (Ar C–F str), 990 (Ar-H bend); ^1H NMR (300 MHz, DMSO-d_6): δ 7.36 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.36 (d, 2H, *J* = 8.4 Hz, Ar-H); 7.73 (d, 2H, *J* = 7.8 Hz, ArH), 7.47 (d, 2H, *J* = 7.8 Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 166.5, 149.1, 143.5, (C=N), 1425, 139.3, 137.1, 136.2, 133.7 130.4, 129.2, 122.4, (ArCs). Anal. Calcd. for $C_{15}H_8ClN_5O_2S$, C, 50.36; H, 2.25; N, 19.57 S, 8.96; found: C, 50.34; H, 2.27; N, 19.56; S, 8.97. EI-MS *m*/*z*: 357 (M^+, 100).

3-(4-Chlorophenyl-)-6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (**5i**): White solid; R_f = 0.68 (petroleum ether:-ethyl acetate 7:3); IR (KBr, cm^{-1}): 3080 (sp^2 CH), 1626 (C=N), 1505 (Ar, C=C), 1266 (N–N=C triazolo-thiadiazole), 669 (C-S-C), ^1H NMR (DMSO-d_6): δ 7.73 (d, 2H, *J* = 7.8 Hz, ArH), 7.47 (d, 2H, *J* = 7.8 Hz, ArH), 7.73 (d, 2H, *J* = 7.8 Hz, ArH), 7.47 (d, 2H, *J* = 7.8 Hz, ArH), ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 165.5, 149.3, 144.5, (C=N), 134.5, 133.3, 132.1, 131.2, 130.7 129.4, 129.2, 128.4 (ArCs). Anal.