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Research Article

COPPER-(*S*)-*N*-METHYLPYRROLIDINE-2-CARBOXYLATE CATALYZED *N*-ARYLATION OF N^5H-1,2,5-THIADIAZOLIDINE 1,1-DIOXIDES

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ABSTRACT

A copper-catalyzed *N*-arylation of N^5H-1,2,5-thiadiazolidine 1,1-dioxides derivatives (cyclic sulfamides) is described. Reactions were carried out using Ullmann–Goldberg-type condensation with *(S)*-N-methyl-2-carboxylate as the ligand, and *N*-arylated products were obtained with moderate to good yields. The structures of the synthesized compounds were confirmed based on analytical and spectral data.

Keywords: Ullmann reaction; Goldberg reaction; *N*-arylation; 1, 2, 5-thiadiazolidine 1, 1-dioxides; aryl halide.

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1. INTRODUCTION

In recent years, 1,2,5-thiadiazolidine 1,1-dioxides and related heterocycles (cyclic sulfamides) have found numerous applications in the fields of biological and medicinal chemistry [1-3]. These compounds serve as inhibitors of serine proteases [4-5], γ-secretases [6], and glycogen

phosphorylase [7], and as starting points for the synthesis of constrained peptides [8]. Consequently, thiadiazolidine rings are also present in the structures of various biologically fused heterocyclic compounds [9].

The *N*-arylation of nitrogen-containing heterocycles has been widely studied. This procedure is an effective method for the formation of *C*(*sp*2)–*N*(*sp*2) bonds, which are difficult to obtain by other routes, and gives access to several *N*-aryl substituted heterocyclic compounds with a wide range of biological activities. Thus, the copper-vicinal diamine-catalyzed reaction of an aryl halide with *N*-nonsubstituted heterocycles in previously reported reactions such as Ullmann coupling condensation [10] and the Goldberg reaction [11] has remained a powerful method for the synthesis of *N*-arylated heterocyclic compounds.

Our studies have focused on the preparation of substituted cyclic sulfamides [12-15]. As a continuation of this research interest, here we report our results regarding the synthesis of *N*-arylthiadiazolidine 1,1-dioxides *via* C(*sp*2)–N(*sp*2) bond formation using (S)-*N*-methylpyrrolidine -2-carboxylate *[(S)-NMPC*] as the suitable ligand (Figure 1) [16-17].

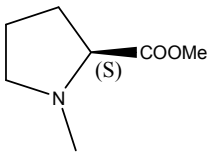
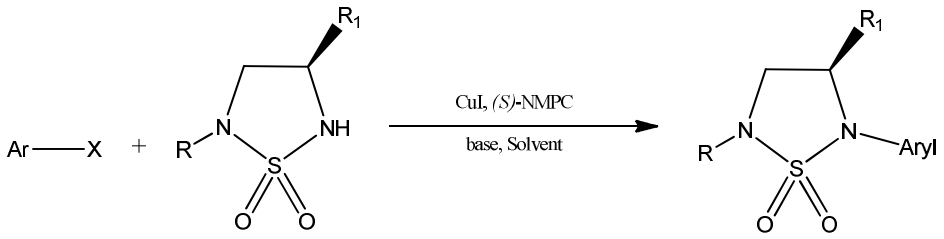


Fig 1. *(S)-N*-methylpyrrolidine-2-carboxylate [(S)-NMPC] as the Ligand for arylation

Starting N^2-substituted, N^5H -1,2,5-thiadiazolidines were prepared from the chlorosulfonyl isocyanate (CSI) according to established synthetic procedures [12-15, 18-20].

2. RESULTS AND DISCUSSION

Here we describe the synthesis of N^2-substituted, N^5-aryl-1,2,5-thiadiazolidine 1,1-dioxides. The copper-(S)-*N*-methylpyrrolidine-2-carboxylate catalyzed system (CuI: 5 mol %, (S)-NMPC: 10 mol %) is very effective for the cross-coupling of N^2-substituted, N^5H-1,2,5-thiadiazolidine 1,1-dioxides by aryl halides with anhydrous (K_3PO_4 or Cs_2CO_3) as the base, in various aprotic solvents (toluene, dioxane, DMF, DMSO) under reflux conditions [16]. The N-arylation pathways were shown in Sceme 1.



2a-j

1a: R= Boc, R_1= H
1b: R= COOMe, R_1=H
1c: R= H, R_1= H
1d: R= Boc, R_1= Me
1e: R= COOMe, R_1= Bn
1f: R= Me, R_1= H

Scheme 1. Synthetic route for Copper-(S)-NMP–catalyzed *N*-arylation of N^5H-1,2,5-thiadiazolidine 1,1-dioxides.

The products were extracted with methylene chloride and purified by column chromatography as necessary to afford pure N^2-substituted, N^5-aryl-1,2,5-thiadiazolidine 1,1-dioxides. The results in Table 1 show that all N^5-arylthiadiazolidine 1,1-dioxydes derivatives **2a–j** were obtained in moderate to good yields within 5–10 hours.

Table 1. Copper-catalyzed *N*-arylation of N^5H-1,2,5-thiadiazolidine 1,1-dioxides with aryl halides.

Products	***Starting sulfamide***	***Arylhalide Ar-X***	***Base/Solvent***	***Ligand***	***T°C/time***	***Yield (%)***
2a	***1a***	Iodobenzene	K_3PO_4/DMF	*(S)-NMPC*	120/5	71
2a	***1a***	Chlorobenzene	K_3PO_4/DMF	*(S)-NMPC*	120/6	19
2a	***1a***	Bromobenzene	K_3PO_4/DMF	*(S)-NMPC*	120/5	36
2b	***1b***	1-iodo-4-nitrobenzene	K_2CO_3/DMSO	*(S)-NMPC*	110/5	53
2b	***1b***	1-iodo-4-nitrobenzene	Cs_2CO_3/DMSO	*(S)-NMPC*	110/5	69
2c	***1b***	5-iodo-1,2,3-trimethoxybenzene	Cs_2CO_3/Dioxan	*(S)-NMPC*	110/6	48
2d	***1a***	3-bromoanisole	K_2CO_3/ Dioxan	*(S)-NMPC*	110/6	38
2d	***1a***	3-bromoanisole	Cs_2CO_3/ PhMe	*(S)-NMPC*	110/10	29
2e	***1b***	1-Iodo-3,5-bis(trifluoromethyl) benzene	K_3PO_4/PhMe	*(S)-NMPC*	110/9	19
2f	***1a***	4-Bromobenzonitrile	K_2CO_3/Dioxan	*(S)-NMPC*	110/6	53
2g	***1a***	1-Iodonaphthalene	K_3PO_4/DMSO	*(S)-NMPC*	110/6	67
2h	***1a***	1-Bromo-4-iodobenzene	Cs_2CO_3/Dioxan	*(S)-NMPC*	110/7	51
2i	***1c***	Iodobenzene (bis arylation)	Cs_2CO_3/Dioxan	*(S)-NMPC*	110/7	48
2j	***1c***	Iodobenzene	Cs_2CO_3/Dioxan	*(S)-NMPC*	110/7	13

We investigated a range of conditions to optimize formation of arylated thiadiazolidine 1,1-dioxides derivatives **3a–j**. As indicated in Table 1, we investigated the effects of various aryl halides (iodobenzene, bromobenzene, and chlorobenzene) under the same conditions (DMF, *(S)*-NMPC, K_3PO_4). The use of aryl iodides as arylating agents in DMF led to the most efficient arylation (71%). Moreover, we also studied the effects of basic conditions in the presence of Cs_2CO_3 and K_2CO_3 (compound **2b**). The optimal yield (69%) was obtained with Cs_2CO_3. Using 1-iodo-3,5-bis(trifluoromethyl)benzene in PhMe led to low yields of the desired products **2d** (29%) and **2e** (19%) over 9–10 hours.

The similar condensation was applied to 2,5-dihydrothiadiazolidine 1,1-dioxides (**1c**) with

iodobenzene in dioxane, using cesium carbonate as the base. This reaction furnished 2,5-diphenyl-1,2,5-thiadiazolidine 1,1-dioxides in 48% as well as 2-phenyl-5-hydro-1,2,5-thiadiazolidine 1,1-dioxides in 13% yields (**Table 1**).

Arylation of non-*N*-substituted thiadiazolidines **1a–c** was confirmed by interpretation of their FT-IR, ^{1}H-NMR, and mass spectra. In the IR spectra of compounds **2a–j**, the absorption peak corresponding to the stretching vibration of the N-H group disappeared, indicating that the amino groups in the non-N-substituted thiadiazolidine had participated completely in the arylation reaction. The ^{1}H-NMR spectra of the N^{5}-arylated thiadiazolidine 1,1-dioxides derivatives **2a–j** showed sharp signals near 7 ppm indicating the presence of aromatic protons. ESI-MS spectra of the compounds **2a-j** showed ion peaks due to [M+Na]+.

3. CONCLUSION

Here we presented a simple, efficient procedure for *N*-arylation and bis-arylation of $N^{5}H$-1,2,5-thiadiazolidine 1,1-dioxides derivatives using (S)-*N*-methylpyrrolidine 2-carboxylate as the suitable ligand under Ullmann–Goldberg-type reaction conditions. This cross-coupling method has the potential to be applied for the insertions of aryls species into a wide range of nitrogen-containing heterocycles.

3. EXPERIMENTAL PROCEDURES

3.1. General

Solvents and starting compounds were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at 300 MHz and 75 MHz, respectively. The chemical shifts, δ, are reported in parts per million (ppm) and were measured in $CDCl_3$ relative to TMS, which was employed as the internal standard. Infrared spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. The mass spectra were obtained using an HP 5989A instrument at 70 eV (for the EI spectra) and using methane as the reagent gas (for CI spectra). ESI-MS spectra were obtained on Mariner (ESI TOF) and API 365 (ESI 3Q) mass spectrometers using methanol as the spray solvent. Melting points (Mp) were determined using a Reichert Thermovar or an Electrothermal 9200 apparatus and are

uncorrected.

3.1. General Procedure for copper catalyzed *N*-arylation of N^2-substituted, N^5-*H*-1,2,5-thiadiazolidine 1,1-dioxides using (S)-*N*-methylpyrrolidine-2-carboxylate.

To a solution of N^2-substituted, N^5H-1,2,5-thiadiazolidine 1,1-dioxides (10 mmol), base (K_3PO_4, Cs_2CO_3,...), S)-NMPC (1 mmol), and CuI (0.5 mmol) in dry organic solvent (DMF, DMSO, dioxane, …) (20 mL) in a 100 mL round-bottom flask was slowly added an aryl halide (12 mmol). The mixture was stirred in an oil bath at the appropriate temperature for 5–10 hours under an argon atmosphere. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature (r.t.) and diluted with EtOAc. The filtrate was washed with 1M HCl (2 × 10 mL) and water (2 × 10 mL) and dried over $MgSO_4$, and then the solvent was removed under reduced pressure to give the crude oil. Flash chromatography (silica gel–CH_2Cl_2) furnished the pure N^2-substituted, N^5-aryl-1,2,5-thiadiazolidine 1,1-dioxides in moderate to good yields.

***2-tert*-butoxycarbonyl, *5*-phenyl-1,2,5-thiadiazolidine 1,1-dioxides (2a)**

Compound **2a** was prepared using **1a** and was obtained as a white solid in 71% yield using iodobenzene, 19% yield using chlorobenzene and 36% yield using bromobenzene. R_f=0.29 (SiO_2, CH_2Cl_2); IR (KBr, *v* cm−1): 1731(C=O), 1150 and 1361(SO_2); ^{1}H NMR (300 MHz, $CDCl_3$): 7.40–7.30 (m, 5H, Ph), 4.00 (t, 2H, C**H**$_2$), 3.4(t, 2H, CH_2), 1.43 (s, 9H, Boc); HRMS ESI+: *m/z*:305 [M+Na]+: $C_{13}H_{18}N_2O_4SNa$+.

2-methyl carboxylate-5-(4-nitrophenyl)-1,2,5-thiadiazolidine 1,1-dioxides (2b) [18]

Compound **2c** was prepared using **1b** and was obtained as a white solid in 53% yield using K_2CO_3/DMSO and 69% yield using Cs_2CO_3/DMSO. R_f=0.22 (SiO_2, CH_2Cl_2); IR (KBr, *v* cm−1): 1727 (C=O), 1509, 1433, 1339 and 1163(SO_2), ^{1}H NMR (300 MHz, $CDCl_3$): 8.28 (*dt*, J=9.2, 3.2 Hz, 2H), 7.47 (*dt*, J=8.8, 3.6 Hz, 2 H), 4.05 (*t*, J=6.2 Hz, 2H), 3.98 (*t*, J=6.4 Hz, 2H), 3.88 ppm (s, 3H); HRMS ESI+: *m/z*:324 $[M+Na]^+$: $C_{10}H_{11}N_3O_6SNa^+$.

2*-methyl carboxylate-*5-(3,5-trifluoromethylphenyl)-1,2,5-thiadiazolidine 1,1-dioxides (2e) [18]

Compound **2e** was prepared using **1b** and was obtained as a white solid in 19% yield. R_f=0.40 (SiO_2, CH_2Cl_2); IR (KBr, *v* cm−1): 2958 C-H aromatics, 1733 (C=O), 1390 and 1173 (SO_2);

^{1}H NMR (300 MHz, $CDCl_3$): d=7.89 (s, 1H), 7.86 (s, 2H), 4.04 (m, 2 H), 3.98 (m, 2 H), 3.88 ppm (s, 3H); HRMS ESI+: *m/z*:415 $[M+Na]^+$: $C_{10}H_{11}N_3O_6SNa^+$.

***2*-methyl carboxylate-*5-(3,4,5-trimethoxyylphenyl)*-1,2,5-thiadiazolidine 1,1-dioxides (2c)** [18]

Compound **2c** was prepared using **1b** and was obtained as a white solid in 48% yield. R_f=0.14 (SiO_2, CH_2Cl_2); IR (KBr, *v* cm−1): 2942, 2837 C-H aromatics, 1713(C=O), 1326 and 1112(SO_2); ^{1}H NMR (300 MHz, $CDCl_3$): 6.64 (s, 2 H), 3.97 (t, J= 6.4 Hz, 2 H), 3.85 (s, 3 H), 3.83 (m, 2H), 3.82 (s, 6H), 3.72 ppm (s, 3H); HRMS ESI^+: *m/z*:369 $[M+Na]^+$: $C_{13}H_{18}N_2O_7SNa^+$.

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