DOI:10.7598/cst2016.1197
ISSN:2278-3458

Chemical Science Transactions
2016, **5(2),** 321-324

RESEARCH ARTICLE

Synthesis of Diaryl Disulfides, Sulfides and Aryl Alkyl Sulfides from Isothiazolones

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Received 24 December 2015 / Accepted 8 January 2016

Abstract: Diaryl disulfides, sulfides and aryl alkyl sulfides were synthesized from isothiazolones**.** This method expedient and high yielding procedure for diaryl disulfides, sulfides and aryl alkyl sulfides under different reaction conditions. The structure of the compounds was determined with NMR, Mass Spectrometry and Infrared Spectroscopy.

Keywords: Isothiazolones, Diaryl Disulfides, Unsymmetrical Sulfides.

Introduction

Transition metal such as Ni, Cu, Fe *etc.* catalyzed carbon hetero-atom coupling reactions have used as a new tool to synthesize a different series of hetero-atom (S, Se and Te) containing organic molecules[1]. Copper catalyzed synthesis of unsymmetrical diaryl sulfides, diaryl disulfides, arylthiols, arylsulfinamides and copper catalyzed 1,2-hydroxysulfenylation of alkenes has been well established[2,3]. Recently, catalytic methods to synthesize sulfur-nitrogen heterocycles (isothiazolones) have been reported by our group[4]. Mono sulphides and disulphides are importantnt organic moieties found in various biologically active molecules.These molecules had direct application to pharmateutical and agrochemicals. Grignard reaction[5] is one of the easiest procedures to synthesis monosulphides from sulphur nitrogen heterocycles. Sulphur nitrogen hetero cycles can be converted to their respective disulphides simply reducing them by sodium borohydride.

Experimental

*Synthesis of Bis(N-phenylbenzamide)disulfide(**1**)*

2-Phenylbenzo[d]isothiazol-3(2*H*)-one (0.68 g, 3.0 mmol) was dissolved in EtOH (20 mL) and cooled to 0 °C under N_2. To this solution, $NaBH_4$ (0.19 g, 5.0 mmol) was added portion wise. Resulted colorless solution stirred for 30 min at this temperature and then room temperature for 45 min. After this, reaction mixture was poured into a beaker containing crushed ice (40 g) and kept in air for oxidation for 3 h. Standard workup and crystallization from CH_2Cl_2 afforded pale yellow crystalline solid. Yield 0.50 g (73%), mp 240-242 ^oC (245-247 ^oC)[6]. ^{1}H NMR δ 10.6 (s, 2H), 7.78-7.72 (m, 6H), 7.63 (d, J = 8.0 Hz, 2H), 7.54-7.49 (m, 2H), 7.42-7.33 (m, 6H), 7.16-7.09 (m, 2H). ^{13}C NMR δ 170.9, 144.1, 141.7, 139.9, 136.6, 134.0, 133.7, 131.6, 131.5, 129.2, 125.4. ES-MS(ESI) 457.0 ($M + H^+$). IR (plate): 3283, 2924, 1636, 1599, 1528, 1430, 1322, 1256, 1116 cm^{-1}.

*Bis(N-cyclohexylbenzamide) Disulfide (**2**)*

Disulphide **2** was prepared from 2-cyclohexylbenzo[d]isothiazol-3(2*H*)-one using the same procedure used for the compound **1**. Yield 0.74 g (90%), (249 ^oC)[7]. ^{1}H NMR δ 8.25 (d, J = 8.0 Hz, 2H), 7.45 (dd, J = 8.0, 1.5 Hz, 2H), 7.40 (dd, J = 8.0, 1.0 Hz, 2H), 7.28 (dt, J =8.0, 1.5 Hz, 1H), 7.16 (dt, J = 7.5, 1.2 Hz, 1H), 5.32(bs, 2H), 3.71(m, 2H), 1.84 (m, 4H), 1.73 (m, 4H), 1.60 (m, 2H), 1.36-1.26(m, 8H), 1.13 (m, 2H) (^{1}H NMR spectrum shows minor impurities at 8.43, 7.61 and 7.10 ppm and could be due to S-N heterocycle). ^{13}C NMR δ 167.3, 134.3, 133.4, 130.6, 130.4, 128.6, 124.9, 48.7, 32.7, 25.7, 25.2. ES-MS(ESI) 469.1 ($M + H^+$)

*2-(Methylthio)-N-phenylbenzamide (**3**)*

To the reduced reaction mixture of 2-phenylbenzo[d]isothiazol-3(2*H*)-one (at 3.0 mmol scale as described for the synthesis of compound **1**), methyl iodide (0.3 mL, 5.0 mmol) was added at 0 ^oC and resulted reaction mixture was stirred for 30 min. Standard workup and purification by column chromatography on silica gel using hexane/ethyl acetate (8:2) yielded **3** as white crystalline solid. Yield 0.67 g (92%), mp 150-152 ^oC (148-149 ^oC)[6]. ^{1}H NMR δ 8.37 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.45 (t, J =7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR δ 166.0, 137.9, 136.6, 135.3, 131.1, 129.16, 129.09, 128.1, 125.8, 124.6, 120.0, 17.1. IR (plate): 3298, 2923, 1646, 1601, 1542, 1436, 1325, 1252, 1164 cm^{-1}. HRMS (ESI) *m/z* 266.0647 calculated for $C_{14}H_{13}NOS + Na^+$ 266.0612.

*N-Benzyl-2-(phenylthio)benzamide (**4**)*[7]

2-Benzylbenzo[d]isothiazol-3(2*H*)-one (0.79 g, 3.5 mmol) was dissolved in dry THF (15 mL). Phenylmagnesium bromide was synthesized in THF (25 mL) from bromobenzene (0.75 mL, 4.0 mmol) and (187 mg, 4.8 mmol) on 4.0 mmol scale. To the Grignard reagent, 2-benzylbenzo[d]isothiazol-3(2H)-one was added drop wise via syringe at 60 ^oC. After complete addition, resulted milky colored solution was obtained which was heated at 60 ^oC for an additional hour and then poured over crushed ice (50 g). Standard workup and purification by column chromatography using hexane / ethyl acetate (7.5: 2.5) gave white solid. Yield 0.89 g (80%), mp 110-112 ^oC. ^{1}H NMR δ7.71-7.69 (m, 1H), 7.34-7.22 (m, 13H), 6.91-6.75 (m, 1H), 4.61 (d, J = 4.0 Hz, 2H). ^{13}C NMR δ167.6, 137.8, 136.5, 134.6, 134.3, 132.3, 131.7, 130.9, 1S29.5, 129.1, 128.7, 128.0, 127.7, 127.5, 127.1, 44.2. IR (plate): 3298, 3061, 2923, 1643, 1531, 1436, 1306, 1263, 1157, 1024 cm^{-1}. HRMS (ESI) *m/z* 342.0929 calculated for $C_{20}H_{17}NOS$ + Na+ 342.0944.

*N-(4-Methoxyphenyl)-2-(phenylthio)benzamide (**5**)*

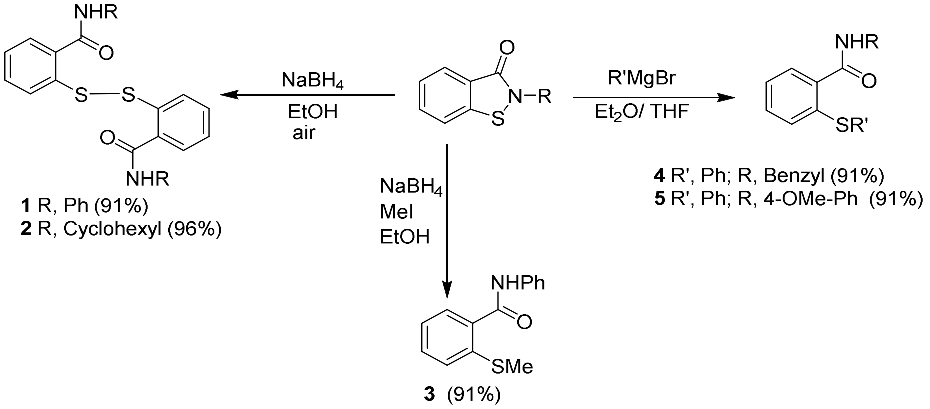
Diaryl sulfide **5** was prepared from 2-cyclohexylbenzo[d]isothiazol-3(2*H*)-one by following similar procedure as described for compound **4** at 4 mmol scale. Purification by column chromatography using hexane / ethyl acetate (8: 2) yielded a white crystalline solid. Yield 1.17 g, (87 %), mp 142-144 ^oC. ^{1}H NMR δ 8.25 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.37-7.29 (m, 9H), 6.87 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR δ 165.6, 156.6, 136.9, 134.52, 134.27, 132.4, 131.7, 131.03, 130.95, 129.54, 129.41, 127.8, 127.4, 121.9, 114.1, 55.6. IR (plate): 3287, 2924, 2852, 1643, 1598, 1513, 1410, 1247, 1175, 1027cm^{-1}. HRMS (ESI) *m/z* 336.1044 and 358.0867 (calcd for $C_{20}H_{17}NO_2S + H^+$: 336.1053 and $C_{20}H_{17}NOS + Na^+$: 358.0872).

Instrumentations

All NMR experiments were carried out on 400 or 500 MHz spectrometers in DMSO-d^{6}or $CDCl_3$ and NMR chemical shifts are reported in ppm referenced to the solvent peaks of $CDCl_3$ 7.26 ppm for ^{1}H and 77.0 (± 0.1) ppm for ^{13}C, respectively) or DMSO-d^{6} (2.50 ppm for 1 H and 39.50 ppm for 13C, respectively). Mass analysis was performed on quadruple-time offlight (Q-TOF) mass spectrometer equipped with an ESI source (+ve). Infrared spectra were recorded as a pellet in KBr with a FTIR machine. Melting points are uncorrected. DMF with sure seal septa, sulphur powder, copper iodide and 1,10-phenanthroline were used as received from Aldrich. Grinded anhydrous K_2CO_3 powder was used which was grinded using mortar, dried in oven at 160 °C for 6 h and stored in a desiccator.

Results and Discussion

To explore the synthetic utility of synthesized isothiazolones, we were able to synthesize corresponding disulfides, unsymmetrical diaryl and aryl alkyl sulfides from synthesized S-N heterocycles (Scheme 1). Diaryl disulfides (**1-2**) and aryl alkyl sulfide (**3**) was obtained by the reduction of S-N bond using $NaBH_4$.



Scheme 1. Synthesis of Diaryl disulfides, -Sulfides and Aryl alkyl sulfides

Aerial oxidation of reduced reaction mixture of gave respective disulfides **1** and **2**, respectively. Addition of methyl iodide to the reduced reaction mixture of 2-phenylbenzo [d]isothiazol-3(2*H*)-one gave methylsulfide **3** in one pot. Quantitative conversion of S-N heterocycles into unsymmetrical diaryl sulfides **4** and **5** has been optimized by employing 1.5 equiv. of Grignard's reagent.

Acknowledgment

We thanks, Department of Chemistry, IIT Bombay for mass and HRMS data collections.

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