DOI 10.5012/bkcs.2010.31.11.3073

A Mild, Efficient and Eco-friendly Synthesis of 1,3-Bis(4-arylthiazol-2-yl)benzenes in PEG-400

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Received August 2, 2009, Accepted April 10, 2010

Key Words: Thioamides, α-Bromoacetophenones, 1,3-Bis(4-arylthiazol-2-yl)benzenes, Polyethylene glycol, Heterocycle

The thiazole ring is an important framework present in a large variety of natural products.[1] Also this moiety is a popular building block for the construction of pharmaceutically interest compounds[2] and has attracted attention of synthetic chemists for over a century.[3] Substitution at the C(2) and C(4) are very frequent and, in some cases, biological activity studies have shown a relationship between the biological activity and the aromatic rings present in those positions.[4] Among them, 2,4-diarylthiazoles are versatile building blocks which potentially have novel therapeutic activities.[5] Within this context, recent efforts towards the synthesis of a subclass with many highly active compounds, including 2,4-thiazolylbenzenesulphonamides (Figure 1) with potent matrix metalloproteinases (MMPs) inhibitors have been reported.[6]

MMPs are a family of Zn-dependent neutral endopeptidases that regulate many biologic processes and have long been associated with cancer-cell invasion and metastasis. Knowing the value of these heterocycles, the preparation of new analogues is of prime importance in both medicinal and synthesis chemistry.

In recent years, the development of eco-friendly organic syntheses is gaining considerable interest both in industrial and academic research. In this context, the replacement of toxic and volatile organic solvents as reaction media by environmentally acceptable alternatives such as H_2O, CO_2, polyethylene glycol (PEG), ionic liquids and carrying out organic reactions under solvent or catalyst-free conditions at ambient temperature is an area of tremendous importance in modern organic synthesis.

Despite of the structural analogy of 1,3-bis(4-arylthiazol-2-yl) benzenes with 2,4-diarylthiazoles, until now they have not been reported extensively in the literature. So, in the course of our recent studies directed toward development of practical, safe and environmentally friendly procedure for some important transformations,[10, 11] herein we are gratified to report a simple, environmentally benign and efficient method for the synthesis of 1,3-bis(4-arylthiazol-2-yl)benzenes *via* double cyclocondensation reaction in PEG 400 at room temperature (Scheme 1).

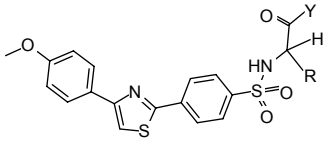
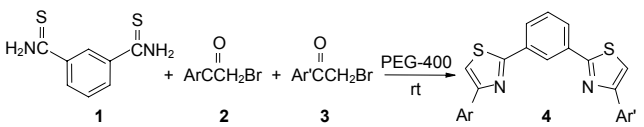


Figure 1



Scheme 1

The experimental procedure is straightforward. The reactions were carried out at room temperature taking a 1:2 molar ratio mixture of 1,3-benzenedithioamide and α-bromoacetophenone in PEG-400 to give the desired products. Thus, a series of 1,3-bis(4-arylthiazol-2-yl)benzenes were prepared as summarized in Table 1. All the products were characterized by ^{1}H-NMR, ^{13}C-NMR, and mass spectral analysis. We found that treatment of arylthioamides with α-bromoacetophenones, carrying either electron-withdrawing or electron-donating groups, afforded the corresponding 1,3-bis(4-arylthiazol-2-yl)benzenes in high to excellent yields in short reaction times (Table 1). To the best of our knowledge, this is the first example of highly efficient synthesis of 1,3-bis(4-arylthiazol-2-yl)benzenes. In addition, the synthesis on a large-scale (20 mmol) was also tested; the reactions demonstrated to be very efficient and the products were obtained in excellent yields using the same reaction conditions as those in the small scale. Inspired with our findings, we continued our study to investigate the synthesis of asymmetry 1,3-bis(4-arylthiazol-2-yl)benzenes. As shown in Table 1, we observed that, the reaction between equally amounts of two different α-bromoacetophenones (1.0 equiv. in each case) and 1,3-benzenedithioamide (1.0 equiv.) afforded only 1,3-di(4'-arylthiazolyl)benzenes under the same conditions in high to excellent yields. Surprisingly, the results show that the reactions took place efficiently, and the selectivities are excellent. Such selectivity has not been reported previously and can be considered a useful practical achievement in 1,3-bis(4-arylthiazol-2-yl)benzenes synthesis.

Table 1. Synthesis of 1,3-bis(4-arylthiazol-2-yl)benzenes in PEG-400 at room temperature

Entry	Ar	Ar'		Time (min)	Yield (%)[a]
1	C_6H_5	C_6H_5	**4a**	30	89
2	4-BrC_6H_4	4-BrC_6H_4	**4b**	40	88
3	4-ClC_6H_4	4-ClC_6H_4	**4c**	40	88
4	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	**4d**	30	92
5	4-$CH_3C_6H_4$	C_6H_5	**4e**	45	82
6	C_6H_5	4-BrC_6H_4	**4f**	40	87
7	4-ClC_6H_4	4-BrC_6H_4	**4g**	50	80
8	4-$CH_3C_6H_4$	4-BrC_6H_4	**4h**	50	83

[a]Yields refer to isolated pure products and were characterized by NMR and MS spectra.

Table 2. Recyclability of PEG-400 in the reaction of 2-bromo-4'-bromoacetophenone, and 1,3-benzenedithioamde[a]

Run	Yield(%)[b]
1	88
2	86
3	84
4	84
5	83

[a]After 40 min. [b]Isolated yields.

This protocol not only affords the products in high to excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. The use of PEG-400 media in this transformation showed rate enhancements, high yields and short reactions times.

The recycling performance of PEG-400 was also investigated in the reaction of 2-bromo-4'-bromoacetophenone and 1,3-benzenedithioamide as a model.[12] The data listed in Table 2 showed that PEG-400 could be reused at least five times.

In conclusion, we have developed a new method that is quite effective and follows an entirely green procedure for the synthesis of 1,3-bis(4-arylthiazol-2-yl)benzenes at room temperature. The mild reaction conditions, operational and experimental simplicity, clean reaction profiles, enhanced reaction rates, and possibility of further transformations of the resulting thiazoles into synthetically interesting and biologically active compounds, make this synthetic methodologies ideally suited for automated applications in organic synthesis.

Experimental

PEG-400 and other chemicals were purchased from Merck Chemical Company and used without further purification. 1,3-Benzenedithioamide was prepared from 1,3-benzenedicarbaldehyde as described in the literature.[11c] Melting points were measured on a Sturt Scientific SMP2 apparatus. Mass spectra were recorded on a Micromass Platform 8379E mass spectrometer operating at an ionization potential of 70 eV. ^{1}H, and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.7 MHz, respectively. Chemical shifts (δ) are given in ppm relative to TMS. Coupling constants are given in Hz.

General procedure. A mixture of arylthioamide (1 mmol) and α-bromoacetophenone (1 mmol) in PEG-400 (4 mL) was stirred at room temperature for the appropriate time according to Table 1. The progress of the reaction was followed by TLC. After completion, the mixture became a solid, which was separated and washed with ice-water. The resulting crude product was recrystallized from EtOH (95%) to afford pure 1,3-bis(4-arylthiazol-2-yl)benzenes.

Compound 4b: Pale yellow solid, mp 208 - 210 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.11 (d, J = 7.7, 2H), 7.91 (d, J = 8.3, 4H), 7.45-7.61 (m, 7H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.23, 155.41, 134.41, 133.32, 131.91, 129.63, 128.18, 128.05, 124.60, 122.34, 113.40. EI-MS: 554 (M^+), 59, 57.

Compound 4e: Pale yellow solid, mp 161 - 164 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.11-8.14 (m, 2H), 8.05 (m, 2H), 7.93 (d, J = 8.1, 2H), 7.54-7.58 (m, 2H), 7.38-7.50 (m, 4H), 7.28 (d, J = 8.1, 2H), 2.42 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 156.57, 167.00, 166.90, 166.87, 138.13, 134.62, 134.55, 134.46, 131.78, 129.52, 129.50, 129.45, 128.76, 128.27, 128.06, 127.98, 126.54, 126.43, 124.64, 112.97, 112.23, 21.28. EI-MS: 410 (M^+), 396, 148, 147, 134, 91, 77.

Compound 4f: Pale yellow solid, mp 168 - 171 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.03-8.14 (m, 4H), 7.90 (m, 2H), 7.37-7.60 (m, 8H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.31, 167.02, 166.92, 156.60, 155.39, 134.61, 134.36, 133.32, 131.90, 129.62, 129.58, 128.78, 128.28, 128.21, 128.18, 128.03, 126.53, 124.61, 122.33, 122.30, 113.40, 113.37, 113.03, 113.00. EI-MS: 475 (M^+), 395, 246, 134, 77, 69.

Compound 4h: Pale yellow solid, mp 207 - 209 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.11 (m, 2H), 7.92 (t, J = 8.2, 4H), 7.48-7.60 (m, 5H), 7.27 (m, 2H), 2.42(s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.22, 166.75, 138.16, 138.11, 134.68, 134.40, 133.32, 131.90, 131.77, 129.62, 129.55, 129.44, 128.20, 128.18, 128.06, 127.97, 127.95, 126.42, 124.61, 122.28, 113.39, 113.34, 112.27, 112.22, 21.27. EI-MS: 489 (M^+), 333, 91, 79.

Acknowledgments. The authors are grateful to the 'Center of Excellence of Chemistry of University of Isfahan (CECUI)' and also the Research Council of the University of Isfahan for financial support of this work.

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12. The reaction of 2-bromo-4'-bromoacetophenone (2.0 mmol), and 1,3-benzenedithioamide (1.0 mmol) was chosen as a model, and recyclability of the media was studied. We found that after the reaction was over and washed with ice-water, the aqueous layer can be dried at 80° for 24 h and reused at least in five runs.