Water Mediated Construction of Trisubstituted Pyrazoles/Isoxazoles Library Using Ketene Dithioacetals

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A small molecule library of alkyl, sulfone, and carboxamide functionalized pyrazoles and isoxazoles has been developed via a rapid sequential condensation of various α-acylketene dithioacetals (**1a**−**o**) with hydrazine hydrate or hydroxylamine hydrochloride, followed by oxidation of sulfide to sulfone using water as the reaction medium. An efficient and safe oxidation of sulfides (**4/5a**−**o**) to the corresponding sulfones (**6/7a**−**o**) using sodium per borate system in aqueous medium is reported. The concise and two step synthesis of trisubstituted pyrazoles and isoxazoles was investigated under variety of reaction condition. The newly developed methodology has the advantage of excellent yield and chemical purity with short reaction time using water as a solvent.

Introduction

In recent decades, combinatorial chemistry tools have enabled the rapid synthesis of a large number of heterocyclic small molecule libraries and it is recognized now as a key element of early drug discovery.[1] The main advantage of the combinatorial technique is the speed at which diverse types of organic compounds can be synthesized, formulated, and tested for a particular application. Moreover, in combinatorial study the quantity of required material is less in comparison to conventional methods, which makes it more suitable when the materials are expensive.[2]

The development of new methods for the synthesis of five member heterocyclic compound libraries, both in solution and in solid phase, is an ever-expanding area in combinatorial chemistry. Specifically, those containing the pyrazole and isoxazole nucleus have been widely used as key building blocks for pharmaceutical agents. Its derivatives are endowed with high pharmacological properties, for example, hypoglycemic, analgesic, anti-inflammatory, antibacterial, anti-HIV, and anticancer activity,[3] as well as useful activities in conditions like schizophrenia, hypertension, and Alzheimer's disease.[4] In addition, they also have agrochemical properties including herbicidal and soil fungicidal activity; thus, they have been used as pesticides and insecticides.[5] Recently, pyrazoles containing aryl substituted emerged as p38 Kinase inhibitors, antiparasitic activities.[6]

Among these, pyrazoles and isoxazoles bearing sulfone and carboxamide moieties demonstrated to have significant pharmacological applications. For examples, cyclooxygenase-2 (COX-2) selective inhibitors, celecoxib (**1**),[7] rofecoxib (**2**),[8] and valdecoxib (**3**)[9] are currently prescribed for the treatment of arthritis and inflammatory diseases (Figure 1, **1**−**3**). These COX-2 inhibitors exhibited anti-inflammatory activity with reduced gastrointestinal side effects. Oxacillin and its derivatives are useful compounds because of their narrow spectrum anti biotic properties[10] (Figure 1, **4**). Recently, pyrrolyl aryl sulfones have been reported by Silvestri et al.[11] and Artico et al.[12] as a new class of human immunodeficiency virus type 1 (HIV-1) RT inhibitors acting at the non-nucleoside binding site of this enzyme. Haruna et al.,[13] have synthesized the propargylic sulfones with various planar molecules and evaluated their DNA binding properties and DNA cleavage activity. Moreover, the 1-(4-methylsulfonyl)benzene and 4-(4-methylsulfonyl)benzene substituted pyrazole compounds containing a nitric oxide donating group at the 3-position of the pyrazole ring, respectively, have been synthesized and evaluated for their ability to inhibit COX isoenzymes in human whole blood.[14] Pyrazoles containing a sulfone group at *N* position have been exhibited promising antimicrobial activity.[15] Furthermore, amide groups linked with isoxazole derivatives are found to

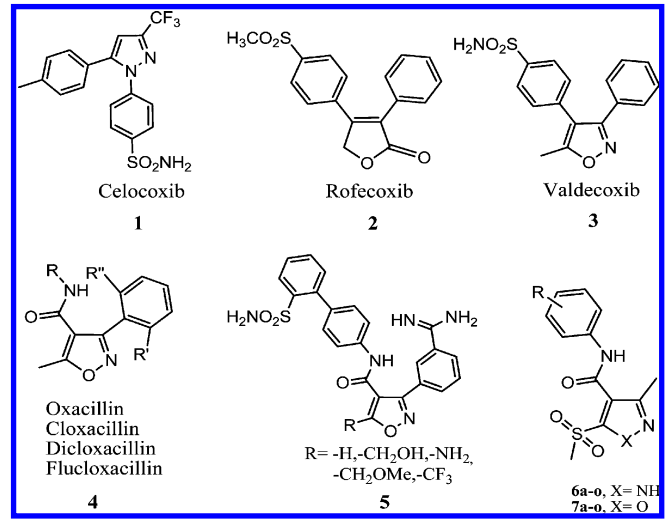

Figure 1. Biologically active pyrazoles and isoxazoles containing alkyl, sulfone, and carboxamide groups (**1**−**5**).

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have combined α_2-adrenoceptor antagonistic and serotonine reuptake inhibiting activities.[16] The isoxazoles containing aryl and carboxamide (Figure 1, **5**) were also shown to have potent in vivo antithrombotic efficacy.[17]

As described above, the tremendous biological potential of the sulfone group and carboxamide group bearing pyrazole and isoxazole scaffolds have attracted many chemists to synthesize this class of molecules. The classical methods to synthesized pyrazoles and isoxazoles involves the condensation of a 1,3-dicarbonyl compound or its synthetic equivalent with hydrazine in appropriate organic solvent.[18] On the other hand, functionalized ketene dithioacetals are versatile intermediates in organic synthesis for the construction of substituted heterocycles such as pyrazoles and isoxazole. The nucleophilic displacement of one of the alkylthio groups from ketene dithioacetals either in an organic solvents or using microwave irradiation which followed by cyclization to afforded the heterocycles.[19] The sulfone group containing synthesis of pyrazoles and isoxazoles library from 2-sulfonylacetonitriles using solid-phase strategy is reported. However, it required a long reaction time, 40 h, and a lengthy workup process.[20] Thus, the practical synthesis of structurally diverse isoxazole/pyrazole based small molecules is of great significance.

Nowadays, a great deal of effort has been focused on the field of green chemistry in adopting methods and processes. As a part of this "green" concept, toxic and/or flammable organic solvents are replaced by alternative non-toxic and nonflammable media. In this context, many efforts have been made to use aqueous media. Among alternative green solvents, water has been the solvent of choice for a variety of transformations.[21] Given the importance of sulfone and carboxamide group containing pyrazoles and isoxazoles, we set out to prepare a small molecule library of 3-methyl-5-(methylsulfonyl)-*N*-aryl-1*H*-pyrazole/isoxazole-4-carboxamide derivatives using ketene dithioacetals in aqueous medium (Figure 1, **6/7a**−**o**).

Herein, we wish to report a novel synthesis of alkyl, methylsulfonyl, and carboxamide functionalized pyrazole or isoxazole heterocyles via condensation of α-acylketene dithioacetals (α-AKDTAs) with hydrazine hydrate or hydroxyl amine hydrochloride and followed by oxidation of sulfide to sulfone using sodium per borate (SPB) in aqueous medium. To our knowledge, this is the first attempt to construct 3-methyl-5-(methylsulfonyl)-*N*-aryl-1*H*-pyrazole/isoxazole-4-carboxamide in solution phase.[19a,22]

Results and Discussions

A series of various α-AKDTAs **1a**−**o** was prepared by some modification in reported procedure.[23] Initially, condensation of α-AKDTA **1a** with hydrazine hydrate **2** took place smoothly in isopropyl alcohol reflux to afford the 3-methyl-5-(methylsulfonyl)-*N*-phenyl-1*H*-pyrazole-4-carboxamide **4a** in good yield (Scheme 1; Entry 1, Table 1). The condensation of **1a** with **2** to generate pyrazole **4a** was investigated using a variety of solvents, as a part of the "green chemistry" concept and to optimize the yield, and the results are summarized in Table 1.

Scheme 1. Synthesis of Trisubstituted Pyrazoles and Isoxazoles in Aqueous Medium

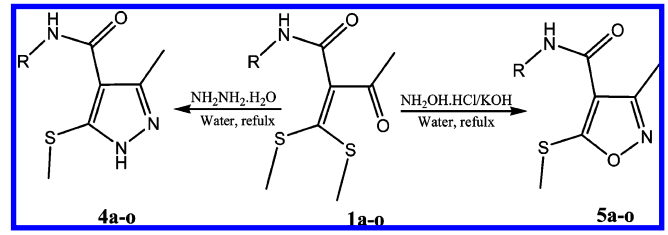


Table 1. Synthesis of 3-Methyl-5-(methylthio)-*N*-phenyl-1*H*-pyrazole-4-carboxamide **4a** Using Variety of Solvents

entry[a]	solvents	time, h	yield[b] %
1	^{i}PrOH	2.8	85
2	MeOH	4.0	81
3	EtOH	3.5	83
4	THF	4.5	79
5	CH_3CN	4.0	75
6	dioxane	3.5	80
7	water	3.0	97

[a] All solution-phase reactions were conducted at reflux temperature of the solvent used. [b] Isolated yield after purification.

The condensation reaction was clean in water, and the yield of desired product was higher (Entry 7, Table 1). On the other hand, the reaction was relatively fast when ^{i}PrOH was used as a solvent with 12% lower yield (Entry 1, Table 1). The yield of desired product was reasonable when MeOH, EtOH, and dioxane were used as a solvent (Entry 2,3,6, Table 1). The other solvents, tetrahydrofuran (THF) and acetonitrile, gave lower yield with higher reaction time (Entry 4,5, Table 1). Thus, it is clear from the aforementioned experiments that the best yield of pyrazoles **4a** could be obtained by employing water as a solvent without using any phase transfer catalyst.

To test the generality of the condensation and to realize the synthesis of a small combinatorial library of substituted pyrazoles and isoxazoles, **15** α-AKDTAs **1a**−**o** were reacted with hydrazine hydrate **2** or hydroxyl amine hydrochloride **3** and potassium hydroxide to furnish pyrazoles **4a**−**o** and isoxazoles **5a**−**o** in excellent yield using water as a solvent (Scheme 1, Table 2). The synthesized compounds were characterized by spectral data. The ^{1}H NMR spectra of compound **4c** displayed characteristic singlet for methyl, mehtylthio, and methoxy hydrogen, respectively, at δ 2.54, 2.64, and 3.92. The two singlets appeared for pyrazole *NH* at δ 10.12 and amide hydrogen at δ 9.62 which revealed the formation of pyrazole ring. However, in ^{1}H NMR of isoxazole **5b** a characteristic singlet for amide proton appeared at δ 9.19 and hydrogen of methylthio group displayed a singlet at δ 2.63.

Because of the remarkable utility of sulfone group in pharmaceuticals and to develop a library of pyrazole and isoxazole functionalized with alkyl, carboxamide, and sulfone, we next planned to oxidize the sulfides to sulfones. Although sulfides can be easily oxidized by a wide variety of oxidizing reagents, unfortunately some of these reagents are not satisfactory for the oxidation of sulfide to sulfone because of low yields of products, toxicity, and expensive reagents or catalysts.[24] The reaction condition for oxidation of sulfide to sulfone was optimized with a variety of oxidizing agent in various solvent (Table 3, Scheme 2).

Table 2. 3-Methyl, 5-Methylthio, 4-Carboxamide Substituted Pyrazoles and Isoxazoles

entry	R	time, h	yield[a] %	mp, °C
4a	Ph	3.0	97	120−122
4b	4-CH_3Ph	3.5	95	125−127
4c	4-CH_3OPh	3.0	96	118−120
4d	4-FPh	2.8	94	132−134
4e	2-CH_3OPh	2.9	92	126−128
4f	2-CH_3	3.2	93	122−124
4g	4-ClPh	3.8	94	128−130
4h	4-EtPh	3.5	95	130−132
4i	4-NO_2Ph	2.5	91	135−137
4j	3-Cl,4-FPh	3.2	90	128−130
4k	5-Cl,2-CH_3OPh	3.0	93	136−138
4l	2,5-diClPh	3.4	89	126−128
4m	2,5-diCH_3Ph	3.2	91	122−124
4n	4-Cl,2-CH_3Ph	2.9	94	121−123
4o	3,4-diFPh	3.2	93	130−132
5a	Ph	2.5	94	135−137
5b	4-CH_3Ph	2.8	92	141−142
5c	4-CH_3OPh	3.0	92	128−130
5d	4-FPh	3.2	90	142−144
5e	2-CH_3OPh	2.6	88	136−138
5f	2-CH_3	3.0	87	133−135
5g	4-ClPh	2.9	89	145−147
5h	4-EtPh	3.3	90	147−148
5i	4-NO_2Ph	2.5	87	149−151
5j	3-Cl,4-FPh	3.4	88	134−136
5k	5-Cl,2-CH_3OPh	3.6	90	151−153
5l	2,5-diClPh	2.8	89	142−144
5m	2,5-diCH_3Ph	2.9	98	136−138
5n	4-Cl,2-CH_3Ph	3.0	87	137−139
5o	3,4-diFPh	3.2	91	146−148

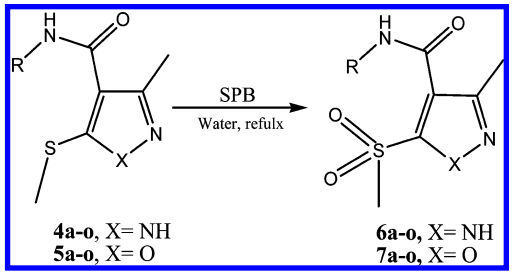
[a] Isolated yield after purification.

Table 3. Optimization of the Reaction Condition for Oxidation of **4a** and **5a** to Its Sulfone

entry[a]	oxidant[b]	solvent	yield[c] % **6a: 7a**	time, min
1	mCPBA	CH_2Cl_2	74:76	125
2	mCPBA	acetone	56:60	95
3	mCPBA	water	65:64	75
4	SPB	CH_2Cl_2	79:82	110
5	SPB	acetone	62:64	95
6	SPB	water	91:94	60
7	SPC	CH_2Cl_2	59:60	120
8	SPC	acetone	52:55	90
9	SPC	water	75:77	60

[a] All solution phase reactions were heated at reflux temperature of the solvent used. [b] Oxidant: mCPBA-2 equiv, SPB-3 equiv, and SPC-3 equiv. [c] Isolated yields after purification.

Scheme 2. Water Mediated Synthesis of Pyrazoles and Isoxazoles Containing Methyl, Sulfone, and Carboxamide Groups



The results gathered in Table 3 indicate that when dichloromethane was used as a solvent the yield of sulfone was higher with *m*-chloroperbenzoic acid (mCPBA) as compared to sodium per carbonate (SPC) and SPB, but it required high reaction time (Entry 1,4,7, Table 3). The yields of desired products were very poor when acetone was used as solvent, and the products were isolated using column chromatography (Entry 2,5,8, Table 3). The best results were obtained when water was used as solvent with the SPB, and the sulfide underwent oxidation to the corresponding sulfone in 45 min with excellent yield (Entry 6, Table 3). However, an excess amount of SPC did not improve yield. When the amount of SPB was reduced, the yield of desired product was lower. The above results indicate, the cheap, environmentally friendly and effective oxidizing agent in water was SPB and gave quantitatively yield of product without use of any activator. With this oxidizing system, all the synthesized compounds **4/5a−o** were oxidized to generate sulfone containing pyrazoles and isoxazole based small molecule library using solution phase synthesis, and the results are gathered in Table 4. The chemical purity of all newly synthesized compounds was examined using UPLC at 254 nm. Among all the final compounds, compounds **6k** and **7l** shown less than 95% chemical purity and other showed more than 95% chemical purity (Figure 2). The ^{1}H NMR spectrum of pyrazole **6j** displayed two characteristic singlets for the methyl and mehtylthio proton, respectively, at δ 2.53 and 3.64. However, two singlets appeared for pyrazole *NH* at δ 12.97 and amide hydrogen at δ 9.61. Compound **7a** displayed a characteristic singlet for amide proton at δ 9.88 and two singlets for methyl and mehtylthio hydrogen, respectively, at δ 2.69 and 3.33. The overall study indicates that this is the simple and facile methodology to introduce sulfone and caboxamide group to pyrazole and isoxazole scaffold in excellent yield and chemical purity.

Table 4. 3-Methyl, 5-Sulfone, 4-Carboxamide Functionalized Library of Pyrazoles and Isoxazoles

entry	R	time, min	yield[a] %	mp, °C
6a	Ph	60	91	168−170
6b	4-CH_3Ph	45	92	172−174
6c	4-CH_3OPh	55	89	166−168
6d	4-FPh	50	88	175−177
6e	2-CH_3OPh	60	90	170−172
6f	2-CH_3	50	94	165−167
6g	4-ClPh	55	89	173−175
6h	4-EtPh	65	92	177−179
6i	4-NO_2Ph	55	92	181−183
6j	3-Cl,4-FPh	50	91	176−178
6k	5-Cl,2-CH_3OPh	50	93	186−188
6l	2,5-diClPh	65	88	176−178
6m	2,5-diCH_3Ph	60	87	170−172
6n	4-Cl,2-CH_3Ph	55	89	171−173
6o	3,4-diFPh	50	85	181−183
7a	Ph	60	94	186−188
7b	4-CH_3Ph	50	95	192−194
7c	4-CH_3OPh	60	93	188−190
7d	4-FPh	55	91	191−193
7e	2-CH_3OPh	65	94	184−186
7f	2-CH_3	55	96	179−181
7g	4-ClPh	60	92	185−187
7h	4-EtPh	65	95	192−194
7i	4-NO_2Ph	60	93	196−198
7j	3-Cl,4-FPh	55	92	188−190
7k	5-Cl,2-CH_3OPh	55	91	195−197
7l	2,5-diClPh	60	90	188−190
7m	2,5-diCH_3Ph	55	91	181−183
7n	4-Cl,2-CH_3Ph	50	88	187−189
7o	3,4-diFPh	65	89	189−191

[a] Isolated yield after purification.

Conclusion

In summary, we have synthesized a solution-phase library of pyrazoles and isoxazoles functionalized with methyl,

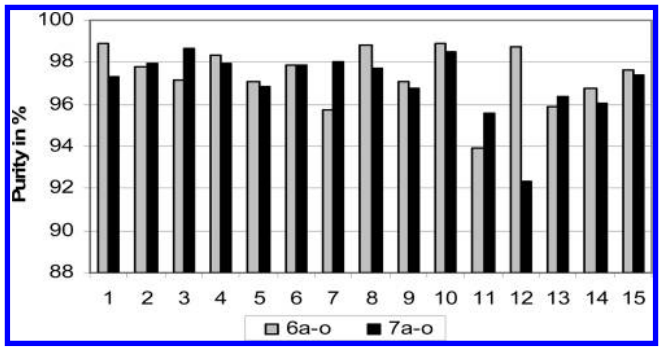


Figure 2. Chemical purity of trifunctionalized pyrazoles and isoxazoles using UPLC at 254 nm.

sulfone and carboxamide moieties in two steps with excellent yield and chemical purity for medicinally interesting molecules. Water emerged as an efficient and green solvent in the condensation reaction of various ketene dithioacetals with hydrazine hydrate or hydroxyl amine hydrochloride. Further, the facile synthesis of sulfone containing pyrazoles and isoxazoles was achieved via oxidation of sulfide to sulfone. A comparative study of various oxidants has been performed, and revealed that SPB is more efficient and effective for oxidation of sulfide to sulfone in aqueous medium. This procedure offers a good scope for the synthesis a wide variety of pyrazoles and isoxazoles containing caboxamide and sulfone in two steps. The present procedure is significant over the existing methods to develop this class of molecules with excellent yield, purity, and simple isolation of products. Currently, we are engaged to make further diversification of pyrazoles and isoxazoles at the C-3 position.

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Supporting Information Available. General experimental procedures for the synthesis of **1-o**, **4/5a−o**, and **6/7a−o**, analytical and spectral characterization data along with IR, Mass, UPLC purity, ^{1}H and ^{13}C NMR spectral copies. This material is available free of charge via the Internet at http://pubs.acs.org.

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