Bull. Korean Chem. Soc. 2009, Vol. 30, No. 12 3085
DOI 10.5012/bkcs.2009.30.12.3085

Solid-phase Synthesis of Novel 7,8-Functionalized Pyrazolo[1,5-a][1,3,5]-2,4-Dithioxotriazine Derivatives on Dithiocarboxy Resin Bound Pyrazoles

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Received September 4, 2009, Accepted October 13, 2009

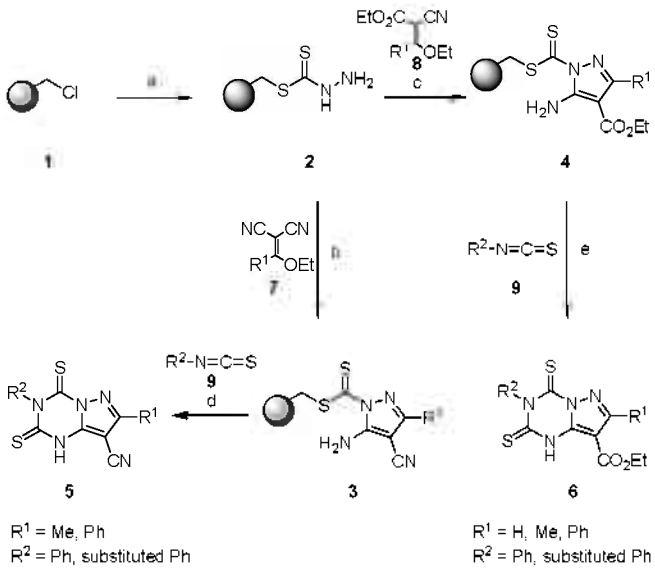
Key Words: Solid-phase synthesis, Pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine, Dithiocarbazate linker, Drug-like library

The five-member ring heterocyclic compounds, which are core components of a large number of substances that possess a wide range of interesting biological activities.[1] In this respect, the potential of the pyrazole scaffold to serve as a privileged structure for the generation of drug-like libraries in drug-discovery programs has been amply demonstrated. The recent success of a pyrazole COX-II (cyclooxygenase) inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry.[2] In addition, the pyrimidinedione and pyrimidinethione ring systems found in quinazolinediones and quinazolinethiones have been used as drug pharmacophores.[3] By using the bioisostere concept, we have designed scaffolds that combine the pyrimidinethione moiety found in quinazolinethiones with the pyrazole ring system. The pyrazolo[1,5-*a*][1,3,5]thioxotriazine bicyclic system, coming from this formulation, is present in substances that are known inhibitors of protein kinase CK2 (casein kinase),[4] phosphodiesterase (PDE4),[5] and DNA gyrase.[6] Another driving force for this combined drug discovery and high throughput organic synthesis program, focusing on drug-like small heterocyclic molecules,[7] is the development of novel modulators of protein kinase CK2 and PDE4 that participate in the control of inflammatory diseases. Since these types of modulators possess pyrazolo[1,5-*a*][1,3,5]triazine functionality, one of the purposes of this effort was the development of a new types of scaffolds, such as the pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine, that might be found in protein kinase inhibitors.

Several reports exist describing the efficient solution-phase synthesis of pyrazolo[1,5-*a*][1,3,5]triazine derivatives that possess drug-like properties.[8] However, methods to readily generate pyrazolo[1,5-*a*][1,3,5]thioxotriazines by employing solid-phase synthesis have not been reported. As a result, we under took an investigation aimed at developing efficient and simple parallel solid-phase synthetic methods to produce various drug-like pyrazolo[1,5-*a*][1,3,5]thioxotriazine derivatives. We previously reported an efficient procedure for the synthesis of a novel 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2-oxo-4-thioxotriazine derivatives.[9] From the previously reported method could be limited only pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine on solid-phase. We needed to come up with an pyrazolo-[1,5-*a*][1,3,5]-2,4-dithioxotriazine for the application of extended library using resin-bound 3,4-functionalized-5-amino-1-dithiocarboxy-pyrazoles **3** and **4** by the reaction of various isothiocyanates.

Here in, we describe the development of an efficient procedure for the synthesis of a novel 7,8-functionalized-pyrazolo-[1,5-*a*][1,3,5]-2,4-dithioxotriazine derivatives **5** and **6** (Scheme 1) through solid phase cyclization reactions of resin-bound 3,4-functionalized-5-amino-1-dithiocarboxy-pyrazoles **3** and **4** with various thiocyanates.

The Merrifield resin **1** was selected as the polymer support used in this investigation. The reaction of this resin **1** with carbon disulfide followed by treatment with hydrazine monohydrate leads to formation of the resin bound dithiocarbazate **2**. We have developed more convenient synthetic rote to the resin **2** compared to the previous report[9] by treatment of hydrazine monohydrate and carbondisulfide with potassium hydroxide in ethanol solvent. In this reaction condition, we could obtain the resin **2** without Fmoc-protection step of hydrazine. Reactions of **2** with



Scheme 1. ***Reagents and conditions***: (a) CS_2, NH_2NH_2·H_2O, KOH, EtOH (1 h), and DMF, 0 °C ~ rt, 4 h. (b) Cyanocarboimidates **7**, Et_3N, CH_3CN, rt, 17 h. (c) Substituted-3-ethoxyacrylonitriles **8**, Et_3N, Dioxane, 80 °C, 17 h. (d) Isothiocyanate **9**, Et_3N, THF, rt ~ 40 °C, 12 h. (e) Isothiocyanate **9**, NaH, THF, rt ~ 40 °C, 12 h.

cyanocarboimidates **7** and 3-ethoxyacrylonitriles **8** gave to the respective polymer-bound 5-amino-1-dithiocarboxy pyrazole resins **3** and **4**.[7c] Finally, the desired taregt 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine derivatives **5** and **6** were liberated from the respective 5-aminopyrazole resins **3** and **4** through the formation of pyrazole thiourea intermediate resin with various aryl isothiocyanates and follows out the intra molecular cyclization reaction.

Table 1. Products, Yields and Purities of 7-Substituted-8-cyanonitrile-1,2,3,4-tetrahydropyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine Derivatives **5**

Product	R^1	R^2	Yield[a] (%)	Purity[b] (%)
5a	Me	Ph	37	98
5b	Me	CO_2Et	10	85
5c	Me	2-MeO-Ph	30	90
5d	Me	3-MeO-Ph	28	98
5e	Me	4-MeO-Ph	36	90
5f	Me	4-F-Ph	35	95
5g	Me	4-NO_2-Ph	34	99
5h	Me	CO_2Et	17	92
5i	Me	Ph	40	98
5j	Me	2-MeO-Ph	39	92
5k	Me	3-MeO-Ph	26	97
5l	Ph	4-MeO-Ph	42	99
5m	Ph	4-F-Ph	46	99
5n	Ph	4-NO_2-Ph	44	92

[a]Three-step overall yields from Merrifield resin **1** (2.0 mmol/g). [b]All of the purified products were checked by LC/MS.

Table 2. Products, Yields and Purities of 7-Substituted-8-ethylcarboxy-1,2,3,4-tetrahydropyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine Derivatives **6**

Product	R^1	R^2	Yield[a] (%)	Purity[b] (%)
6a	H	Ph	53	98
6b	H	2-MeO-Ph	46	98
6c	H	3-MeO-Ph	31	99
6d	H	4-MeO-Ph	55	99
6e	H	4-F-Ph	50	99
6f	H	4-NO_2-Ph	49	95
6g	H	Ph	36	90
6h	H	2-MeO-Ph	30	99
6i	Me	3-MeO-Ph	29	99
6j	Me	4-MeO-Ph	39	95
6k	Me	4-F-Ph	40	99
6l	Me	4-NO_2-Ph	39	99
6m	Me	Ph	46	92
6n	Me	2-MeO-Ph	36	90
6o	Me	3-MeO-Ph	33	90
6p	Me	4-MeO-Ph	45	95
6q	Me	4-F-Ph	49	99
6r	Ph	4-NO_2-Ph	47	95
6s	Ph	Ac	10	85
6t	Ph	Propyl	16	80

[a]Three-step overall yields from Merrifield resin **1** (2.0 mmol/g). [b]All of the purified products were checked by LC/MS.

The progress of all of the solid phase reactions employed in these sequences was monitored by using ATR-FTIR spectroscopy on single beads (Supporting Information S6, S7). For example, the formation of the dithiocarbazate resin **2** was demonstrated by the generation of prominent carbamate bands at 1361 cm^{-1} by ATR-FTIR. And the pyrazole resin **3** could obtain from the dithiocarbazate resin **2** by treated with cyanocarboimidates **7** in acetonitrile. The progress of this reaction was monitored by the appearance of the cyanonitrile stretching band at 2217 cm^{-1}. On the other hand, the cyclization reactions of hydrazine dithiocarbazate resin **2** with substituted-3-ethoxyacrylonitriles **8** proceeded well in 1,4-dioxane solvent, as indicated by the appearance of the ester stretching band of resin bound 5-amino pyrazole **4** at 1685 cm^{-1}.

The concurrent cyclization-resin cleavage reactions of 5-amino pyrazole resins **3** and **4** were progressed in the presence of Et_3N (THF, 40 °C, 12 h) same as concurrent clization reaction conditions with isocyanates.[9] In the case of reactions of the 4-ethylcarboxy-5-amino pyrazole resins **4**, the strong base NaH is required (THF, 40 °C, 12 h) to proceed the first nucleophilc reaction of pyrazole amino group to isothiocyanates. As shown in Table 1 and 2, we could obtain various 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine derivatives **5** and **6** by the concurrent reaction of 5-amino pyrazole resins **3** and **4** with aryl isothiocyanates in good three step overall yields starting from the Merrifield resin with high purities.

In conclusion, the results of the investigation described above demonstrate that 7,8-functionalized pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazine derivatives **5** and **6** can be efficiently prepared by using a concise solid phase synthetic sequence involving the intermediacy of the 5-amino-1-dithiocarboxypyrazole resins **3** and **4**. Cyclization reactions of pyrazole resins **3** and **4**, promoted by treatment with various substituted aryl isothiocyanates results in liberation from the resins of the respective target 7,8-functionalized-pyrazolo[1,5-*a*][1,3,5]-2,4-dithioxotriazines derivatives **5** and **6** in high overall yields and high purities.

Experimental Procedures

General. All chemicals were reagent grade and used as purchased. The Merrifield resin (loading capacity 2.00 mmol/g, 100 ~ 200 mesh) was purchased from BeadTech. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin layer plates or ATR-FRIR analysis using TravelIR™ (SensIR Technology). Flash column chromatography was carried out on Merck silica gel 60 (230 ~ 400 mesh). On solid-phase synthesis, reactions, filteration, and washing were carried out on a Mini-Block (Bohdan) and solvent evaporation was performed on a GeneVac Atlas HT-4 centrifugal vacuum evaporator. The crude products were purified by parallel chromatography using Quad-3™. ^1H NMR and ^{13}C NMR spectra were recorded in d units relative to deuterated solvent as internal reference by Bruker 500 MHz NMR instrument. LC-MS analysis was performed on ESI mass spectrometer with PDA detection. LC-MS area% purities of all products were determined by LC peak area analysis (XTerraMS C18 column, 4.6 mm × 100 mm; PDA detector at 200 ~ 400 nm; gradient, 5 ~ 95% $CH_3CN//H_2O$).

Preparation of dithiocarbazate resin (2). To suspension of

hydrazine mono-hydrate (10.0 mL, 203.15 mmol) in ethanol (100 mL) at 0 °C was added successively carbon disulfide (13.0 mL, 223.46 mmol) with potassium hydroxide (13.5 g, 243.78 mmol) and the mixture was stirred for 1 h. The reaction mixture was formed two layers with light-brown color and then the light-brown layer was dissolved in DMF (150 mL) at 0 °C. And then Merrifield resin **1** (30.0 g, loading capacity 2.0 mmol/g) was added to the previous light-brown DMF solution. The mixture was stirred at rt for 4 h. The resin was filtered, washed several times with CH_2Cl_2, DMF, H_2O and MeOH and dried in a vacuum oven to give dithiocarbazate resin **2** (5.72 g) as an light yellow solid. On-bead ATR-FTIR (cm^{-1}) 3024, 2919, 1600, 1509, 1492, 1450, 1421, 1363, 1180, 1154, 1028, 838, 755, 744, 697.

Preparation of 5-amino-1-dithiocarbamoyl pyrazole resin (3a). To a suspension of dithiocarbazate resin **2** (5.0 g, theoretically 10.0 mmol) in acetonitrile (70 mL) at rt was added 2-(1-ethoxyethylidene)malononitrile (4.1 g, 30.0 mmol) and Et_3N (4.18 mL, 30.0 mmol). The mixture was stirred at rt for 17 h. The resin was filtered, washed several times with DMF, MeOH, CH_2Cl_2 and MeOH, and dried in a vacuum oven. The 5-amino-1-dithiocarbamoyl pyrazole resin **3a** was obtained as a yellow (5.6 g). On-bead ATR-FTIR (cm^{-1}) 3024, 2919, 2215 (CN), 1619, 1602, 1562, 1509, 1492, 1451, 1390, 1357, 1318, 1153, 1029, 991, 637, 757, 697.

Preparation of 7-methyl-3-phenyl-2,4-dithioxo-1,2,3,4-tetrahydro-pyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitrile (5a). To a mixture of 5-amino-1-dithiocarbamoyl pyrazole resin **3a** (300.0 mg, theoretically 0.60 mmol) in DMF (2.0 mL) was added K_2CO_3 (415.0 mg, 3.00 mmol) and phenyl isothiocyanate (342 μL, 1.80 mmol), and the mixture was stirred at 40 °C for 12 h. The resin was filtered and washed with CH_2Cl_2, EtOAc. 4 N HCl (2.0 mL) were added; the filtrate was extracted with EtOAc. The residue was purified by a silica gel column chromatography (10 : 1 mixture of ethyl acetate and *n*-hexane ethyl acetate) to afford the desired product 7-methyl-3-phenyl-2,4-dithioxo-1,2,3,4-tetrahydro-pyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitrilee **5a** (65.0 mg, 37%; 98% purity); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39 (m, 2H), 7.28 (m, 1H), 7.09 (m, 2H), 2.32 (s, 3H); LC/MS (ESI) *m/z* 300 ($[M+H]^+$).

Preparation of 5-amino-1-dithiocarbamoyl pyrazole resin (4a). To a suspension of dithiocarbazate resin **2** (5.0 g, theoretically 10.0 mmol) in dioxane (70 mL) at rt was added ethyl (ethoxymethylene)cyanoacetate (5.0 g, 30.0 mmol) and Et_3N (4.15 mL, 30.0 mmol). The mixture was stirred at 80 °C for 17 h. The resin was filtered, washed several times with DMF, MeOH, CH_2Cl_2 and MeOH, and dried in a vacuum oven. The 5-amino-1-dithiocarbamoyl pyrazole resin **4a** was obtained as a yellow solid (5.84 g). On-bead ATR-FTIR (cm^{-1}) 3409, 3288 (NH_2), 3024, 2920, 1679 (C=O), 1612, 1546, 1509, 1492, 1451, 1423, 1329, 1265, 1232, 1153, 1111, 1066, 1018, 964, 873, 839, 757, 737, 697.

Preparation of 3-phenyl-2,4-dithioxo-1,2,3,4-tetrahydro-pyrazolo[1,5-*a*][1,3,5]triazine-8-carboxylic acid ethyl ester (6a). To a mixture of 5-amino-1-dithiocarbamoyl pyrazole resin **4a** (300 mg, theoretically 0.60 mmol) in THF (3.0 mL) at rt was added 60% dispersion of NaH in mineral oil (72.0 mg, 1.80 mmol) and phenyl isothiocyanate (342 μL, 1.80 mmol), and the mixture was stirred at 60 °C for 12 h. The resin was filtered and washed with CH_2Cl_2, EtOAc. 4 N HCl (2.0 mL) were added; the filtrate was extracted with EtOAc. The residue was purified by a silica gel column chromatography (2:1 mixture of ethyl acetate and n-hexane ethyl acetate) to afford the desired product 3-phenyl-2,4-dithioxo-1,2,3,4-tetrahydro-pyrazolo[1,5-*a*][1,3,5]triazine-8-carboxylic acid ethyl ester **6a** (105 mg, 53%; 98% purity). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.39 (m, 2H), 7.28 (m, 1H), 7.10 (m, 2H), 4.22 (q, 2H, J = 7.08 Hz), 1.27 (t, 3H, J = 7.10 Hz); LC/MS (ESI) *m/z* 333 ($[M+H]^-$).

Acknowledgments. This research was supported by a grant from Seoul Research and Business Development Program (grant number 10574), Korea, and a grant from the Basic Research Program of Dongguk University.

Supporting Information Available. Full experimental procedures, analytical data of compounds, copies of ^{1}H NMR, ^{13}C NMR and LC-MS spectra of compounds **5a-5n** and **6a-6t**, and ATR-FTIR spectra of resins **1-4** are given.

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