Published in final edited form as:

European J Org Chem. 2016 April ; 2016(11): 1968–1971. doi:10.1002/ejoc.201600163.

New Three-Component Bicyclization Leading to Densely Functionalized Pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines

Dr. Wen-Juan Hao^a, Peng Zhou^a, Fei-Yue Wu^a, Prof. Dr. Bo Jiang^{a,b,*}, Prof. Shu-Jiang Tu^a, and Prof. Dr. Guigen Li^{b,c,*}

^aSchool of Chemistry and Chemical Engineering, Jiangsu Normal University, Xuzhou, Jiangsu 221116, (China)

^bDepartment of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States

^cInstitute of Chemistry & BioMedical Sciences, Collaborative Innovation Center of Chemistry for Life Sciences, Nanjing University, Nanjing 210093, P. R. China

Abstract

A novel three-component bicyclization for the efficient synthesis of densely functionalized pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines has been established from readily accessible aryl aldehydes, α -thiocyanate ketones and pyrazol-5-amines. The reaction pathway involves nucleophilic addition/*5-exo-trig*/*6-endo-trig* bicyclization sequence, resulting in continuous multiple bond-forming events including C–N and C–C bonds to rapidly a molecular complexity.

Keywords

Multicomponent Reactions; Bicyclization; Microwave Heating; α -thiocyanate ketones; Pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines

Introduction

The pursuit of maximizing synthetic efficiency continues to demand tremendous efforts aimed at remarkably selective control of forming complex cyclic structures with important biological significances.^[1] Multicomponent reactions (MCRs) have emerged as one of the most effective strategies for the assembly of complex structural frameworks by the combination of two or more distinct reactions into a one-pot transformation in an environmentally benign and atom-economic fashion.^[2,3] As a branch of multi-component reactions, multicomponent bicyclizations are highly attractive due to their annulation efficiency, bond-forming efficiency and high levels of structural complexity.^[4] Specifically, multicomponent bicyclizations can avoid tedious steps of protection and deprotection of functional groups and isolation of intermediates, thereby minimizing the generation of waste and rendering the transformations green.^[5] In recent years, enormous efforts have been paid

on the establishment of various multicomponent bicyclizations toward polycyclic structures with biological interests.^[6] However, the utilization of three-component bicyclizations for the construction of densely functionalized pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines from readily available starting materials, to the best of our knowledge, has not yet been reported.

Systems containing fused thiazole and pyrimidine units take a significant position in organisms because of their biological potentials. Among them, thiazolo[3,2-*a*]pyrimidine moiety is one of the significant core structures, which has been known to display a wide range of biological activities such as anti-HSV-1 activity,^[7] acetylcholinesterase inhibitors^[8] and platelet aggregation inhibitors.^[9] Furthermore, thiazolo[3,2-*a*]pyrimidines were extensively used as a pharmaceutical core, represented by ritanserlin and setoperone.^[10] Compounds incorporated both thiazolo[3,2-*a*]pyrimidine and pyrazole motifs exhibited xanthine oxidase (XO) inhibitory activity.^[11] The biological importance of these compounds inspired our interest in creating methodologies for their syntheses.

α -Thiocyanate ketones are types of competent reactants endowed with multiple reactive sites, that would be used as versatile and synthetically useful building blocks for the synthesis of functional molecules.^[12] As part of our continuing interest in the design of new bicyclizations,^[13] we reasoned that under suitable conditions, nucleophilic addition of nucleophiles (Nu) into reactive cyano group of α -thiocyanate ketones occurs to afford thiazoles with two nucleophilic sites through 5-*exo-trig* cyclization and dehydration, followed by treatment with electrophiles (E) to give bicyclic products (Scheme 1). Based on this analysis, we used pyrazol-5-amines having two reactive sites as nucleophiles and aryl aldehydes as electrophiles (E) to treat with α -thiocyanate ketones to evaluate the feasibility of the formation of pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines (Scheme 2). As per our expectation, this three-component reaction readily proceeded to give the expected tricyclic product under microwave (MW) heating. Herein, we would like to report this interesting transformation.

Results and Discussion

Our strategy of synthesizing the functionalized pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines was through a three-component reaction of aryl aldehydes **1** with the preformed α -thiocyanate ketones **2** and pyrazol-5-amines **3**. The preparation of α -thiocyanate ketones **2** was commonly achieved by nucleophilic substitution of α -halogenated aryl ketones with thiocyanate salts in hydroalcoholic media.^[14] The initial experiments were performed with 4-chlorobenzaldehyde (**1a**), 1-(4-nitrophenyl)-2-thiocyanatoethan-1-one (**2a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**) in DMF at 90 °C under microwave irradiation for 25 min. This set of conditions lead to the expected pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidine product **4a**, albeit with a low 32% yield (Table entry 1). Encouraged by this preliminary result, we further optimized the reaction conditions. The solvent effect was first investigated (compare entries 1–8). The use of HOAc facilitated this transformation, delivering a higher 51% chemical yield of **4a**, whereas tetrahydrofuran (THF), water, benzene or dichloromethane (DCM) served as reaction media completely suppressed the reaction process. Another two solvents including EtOH and CH₃CN were proven ineffective, giving inferior outcomes compared with HOAc (entry 2 vs. entries 7 and 8). Afterward, we

attempted to adjust the reaction temperatures to improve the reaction efficiency. Elevating the temperature to 120 °C proved more efficient, affording the expected **4a** in 65% yield (entry 10). The yield leveled off when the temperature was further increased (entry 11). Gratifyingly, the reaction of **1a** with **2a** and **3** in a 1.2:1:1.2 mole ratio worked more efficiently, resulting in a 77% chemical yield (entry 12). The identical reaction was investigated under classical heating conditions at 120 °C for 90 min, which provided a 65% yield of **4a** (entry 13).

Under the above optimized conditions, the substrate scope of this three-component bicyclizations was examined by using readily available starting materials. As revealed in Table 2, α -thiocyanate ketones **2a** was first subjected to the reaction of **3** and aryl aldehydes with different electronic properties under microwave irradiation without use of any strong acid or metal catalyst, and the expected pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines **4a–4i** were obtained in good yields. Various aryl aldehydes having substituents at different positions with electron-poor (fluoro, chloro, bromo), electron-neutral (H), and electron-rich (methyl, methoxy) groups were compatible. Sterically encumbered, 2-bromophenyl (**1d**) and 2,3-dimethoxyphenyl (**1h**) aldehydes were found to have no influence on the course of the reaction, with tricyclic products **4d** and **4h** being afforded in 67% and 58% yields, respectively. Next, we selected 3-nitrophenyl and phenyl substituted α -thiocyanate ketones **2b** and **2c** as representative substrates to further expand the synthetic utility of this methodology. As we had expected, these reactions proceeded smoothly to give access to the corresponding tricyclic products. **4j–4s**, which are normally difficult to prepare by other methods. The presence of electron-withdrawing substituents (fluorine, chlorine, bromine, nitro) at *para*-position of aryl aldehydes seemed to improve the efficiency of the reaction, as the corresponding products **4j** and **4n–4q** could be isolated in slightly higher yields (Table 2, entries 10 and 14–17). Regrettably, when substrate **2** with an electron-donating methoxy group was used, this reaction gave complex mixture. It is worth mentioning that during present domino bicyclization process, the thiazole and pyrimidine rings have been simultaneously constructed in a one-pot intermolecular manner, and up to four σ bonds including three C-N were also formed. This observation is very interesting in organic synthesis. Besides, the present protocol also showed *the following attractive characteristics*: (1) fast reaction rates which enable the reaction to be completed within 20–30 min; (2) eco-friendly process in which water is a major byproduct; (3) readily available starting materials in which six reactive sites are synergistically utilized.

The resulting pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines **4** were fully characterized by their NMR spectroscopy and HRMS. Furthermore, in the case of product **4b**, its structure was unambiguously confirmed by X-ray diffraction.

On the basis of the above observations, a reasoned mechanism has been proposed for the formation of pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines **4** as shown in Scheme 3. Due to the high reactivity of thiocyanate group, a cascade nucleophilic addition / 5-*exo-trig* cyclization between α -thiocyanate ketones **2** and pyrazol-5-amines **3** occurs, leading to thiazole intermediate **A**, followed by the reaction with aromatic aldehydes **1** to generate intermediate **B**. This intermediate then undergoes dehydration and intramolecular 6-*endo-trig* cyclization

to yield intermediate **D**, which is converted into the final products **4** through proton transfer (Scheme 3).

Conclusions

We have established a new three-component bicyclizations of α -thiocyanate ketones under mild and metal-free reaction conditions leading to biologically interesting tricyclic pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines. A significant feature of the developed process enables cascade-type formation of successive C–N and C–C bonds through a successive nucleophilic addition/5-*exo-trig* cyclization/ 6-*endo-trig* cyclization sequence and represents a new bicyclization strategy for the construction of *N,S*-containing heterocycles. Currently, further efforts on the evaluation of their bioactivity are underway in our laboratory

Experimental Section

Aryl aldehyde **1** (1.2 mmol) was introduced in a 10 mL Initiator reaction vial; aryl-2-thiocyanato-ethanone **2** (1.0 mmol), pyrazol-5-amines **3** (1.2 mmol) and HOAc (2.0 mL) were then successively added. Subsequently, the reaction vial was capped and then pre-stirred for 20 s. The mixture was irradiated (time, 20–30 min; temperature, 120 °C; absorption level, high; fixed hold time) until TLC revealed that conversion of the starting material **2** was complete. The system was diluted with cold water (40 mL). The solid product was collected by Büchner filtration and purified by flash column chromatography (silica gel, mixtures of petroleum ether/ethyl acetate) to afford the pure product **4**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful for financial support from the NSFC (Nos. 21332005, 21232004, and 21472071), PAPD of Jiangsu Higher Education Institutions, the Outstanding Youth Fund of JSNU (YQ2015003), NSF of Jiangsu Province (BK20151163), NSF of Jiangsu Province (15KJB150006), Robert A. Welch Foundation (D-1361, USA), NIH (R33DA031860, USA), and NSF of JSNU (14XLR005).

References

1. a) Padwa A. Chem. Soc. Rev. 2009; 38:3072. [PubMed: 19847342] b) Toure BB, Hall DG. Chem. Rev. 2009; 109:4439. [PubMed: 19480390] c) Tietze LF, Kinzel T, Brazel CC. Acc. Chem. Res. 2009; 42:367. [PubMed: 19154154]
2. For reviews, see: Groenendaal B, Ruijter E, Orru RVA. Chem. Commun. 2008:5474. Padwa A. Chem. Soc. Rev. 2009; 38:3072. [PubMed: 19847342] Tietze LF, Kinze T, Brazel CC. Acc. Chem. Res. 2009; 42:367. [PubMed: 19154154] Dömling A, Wang W, Wang K. Chem. Rev. 2012; 112:3083. [PubMed: 22435608] Ruijter E, Scheffelaar R, Orru RVA. Angew. Chem., Int. Ed. 2011; 50:6234. Jiang B, Rajale T, Wever W, Tu S-J, Li G. Chem.-Asian J. 2010; 5:2318. [PubMed: 20922748]
3. a) Tietze, LF., Brasche, G., Gerike, K. Domino Reactions in Organic Chemistry. Weinheim, Germany: Wiley-VCH; 2006. b) Zhu, JP., Bienaymé, H., editors. Multicomponent Reactions. Weinheim, Germany: Wiley-VCH; 2004. c) Toure BB, Hall DG. Chem. Rev. 2009; 109:4439. [PubMed: 19480390] d) Ganem B. Acc. Chem. Res. 2009; 42:463. [PubMed: 19175315] e)

- Ismabery N, Lavila R. Chem-Eur. J. 2008; 14:8444. [PubMed: 18576454] f) Tietze LF. Chem. Rev. 1996; 96:115. [PubMed: 11848746]
4. a) Li M, Shao P, Wang S-W, Kong W, Wen L-R. J. Org. Chem. 2012; 77:8956. [PubMed: 22970749] b) Terzidis MA, Zarganes-Tzitzikas T, Tsimenidis C, Stephanidou-Stephanatou J, Tsoleridis CA, Kostakis GE. J. Org. Chem. 2012; 77:9018. [PubMed: 22978377] c) Jiang B, Fan W, Sun M-Y, Ye Q, Wang S-L, Tu S-J, Li G. J. Org. Chem. 2014; 79:5258. [PubMed: 24833111] d) Gao Q, Hao W-J, Liu F, Tu S-J, Wang S-L, Li G, Jiang B. Chem. Commun. 2016; 52:900.e) Wan J-P, Lin Y, Huang Q, Liu Y. J. Org. Chem. 2014; 79:7232. [PubMed: 25003698] f) Fan W, Ye Q, Xu H-W, Jiang B, Wang S-L, Tu S-J. Org. Lett. 2013; 15:2258. [PubMed: 23597067]
5. a) Tian Y, Tian L, He X, Li C-J, Jia X, Li J. Org. Lett. 2015; 17:4874. [PubMed: 26357837] b) Jiang B, Wang X, Xu H-W, Tu M-S, Tu S-J, Li G. Org. Lett. 2013; 15:1540. [PubMed: 23506186] c) Jia S, Su S, Li C, Jia X, Li J. Org. Lett. 2014; 16:5604. [PubMed: 25313935] d) Jiang B, Tu S-J, Kaur P, Wever W, Li G. J. Am. Chem. Soc. 2009; 131:11660. [PubMed: 19722590] e) Jia F-C, Xu C, Cai Q, Wu A-X. Chem. Commun. 2014; 50:9914.
6. a) Raikar SN, Malinakova HC. J. Org. Chem. 2013; 78:3832. [PubMed: 23521584] b) Xia L, Li S, Chen R-J, Liu K, Chen X-C. J. Org. Chem. 2013; 78:3120. [PubMed: 23442048] c) Wang X, Wang S-Y, Ji S-J. Org. Lett. 2013; 15:1954. [PubMed: 23565712] d) Qian W-Y, Amegadzie A, Winternheimer D, Allen J. Org. Lett. 2013; 15:2986. [PubMed: 23751086] e) Xu Z-G, Moline FD, Cappelli AP, Hulme C. Org. Lett. 2013; 15:2738. [PubMed: 23718233]
7. Mohamed SF, Flefel EM, Amr AE-GE, Abd E-S, Dina N. Eur. J. Med. Chem. 2010; 45:1494. [PubMed: 20110135]
8. Alam O, Khan SA, Siddiqui N, Ahsan W. Med. Chem. Res. 2010; 19:1245.
9. Lee, CS., Lee, TH., Yoon, SK., Choi, JS., Jang, YJ., Kim, SW., Chang, HK., Park, MJ., Kim, TH., Ahn, YH., Park, HD., Park, HJ., Lim, DC., Lee, JY., Lee, SH., Park, WS., Oh, YS. PCT Int. Appl. WO 2010027236. 2010. Chem. Abstr. 152, 358057, 2010
10. a) Kennis, LEJ., Vandenberk, J., Mertens, JK. E.P. Patent 110,435. 1984. Chem. Abstr. 1985, 102, 594b) Den Boer JA, Vahlne JO, Post P, Heck AH, Daubenton F, Olbrich R. Human Psychopharmacol. Clin. Exp. 2000; 15:179.c) Back T, Prado R, Zhao WZ, Watson BD, Ginsberg MD. Neurol. Res. 1998; 20:643. [PubMed: 9785594] d) Cornish JW, Maany I, Fudala PJ, Ehrman RN, Robbins SJ, O'Brien CP. Drug Alcohol Depend. 2001; 61:183. [PubMed: 11137283]
11. Khobragade CN, Bodade RG, Dawane BS, Konda SG, Khandare NT. J. Enzy. Inhib. Med. Chem. 2010; 25:615.
12. a) Xu H-W, Ma G-H, Jiang B, Tu S-J. Synthesis. 2013; 45:3392.b) Wang X, Wu Q, Jiang B, Fan W, Tu S-J. Tetrahedron Lett. 2014; 55:21.c) Wu F-Y, Li Y, Feng H, Wu Q, Jiang B, Shi F, Tu S-J. Synthesis. 2011; 43:2459.d) Bisogno FR, Cuetos A. Green Chem. 2009; 11:452.e) El-Din AS. Sulfur Lett. 2003; 26:35.f) Jiang B, Tu X-J, Wang X, Tu S-J, Li G. Org. Lett. 2014; 16:3656. [PubMed: 24988049]
13. a) Qiu J-K, Jiang B, Zhu Y-L, Hao W-J, Wang D-C, Sun J, Wei P, Tu S-J, Li G. J. Am. Chem. Soc. 2015; 137:8928. [PubMed: 26131954] b) Chen Z-Z, Liu S, Xu G, Wu S, Miao J-N, Jiang B, Hao W-J, Wang S-L, Tu S-J, Li G. Chem. Sci. 2015; 6:6654. [PubMed: 26568814] c) Gao Q, Zhou P, Liu F, Hao W-J, Yao C, Jiang B, Tu S-J. Chem. Commun. 2015; 51:9519.d) Jiang B, Ye Q, Fan W, Wang S-L, Tu S-J, Li G. Chem. Commun. 2014; 50:6108.
14. Bisogno FR, Cuetos A, Lavandera I, Gotor V. Green Chem. 2009; 11:452.
15. Crystal data for **4b** (CCDC 1457720): C₂₆H₁₈BrN₅O₂S, *Mr* = 544.42, Monoclinic, space group P2(1)/c, *a* = 15.1033(18) Å, *b* = 10.9244(12) Å, *c* = 15.2630(17) Å, *V* = 2393.7(5) Å³, *T* = 293(2) K, *Z* = 4, 11857 reflections measured, 4211 unique (*R*_{int} = 0.2773) which were used in all calculation, *R*₁ = 0.0645, *wR*₂ = 0.0722.

Figure 1.
X-Ray Structure of **4b**^[15]

Scheme 1.
The Design of Bicyclization Reaction

Scheme 2.
The Synthesis of Tricyclic Products **4**

Scheme 3.
Proposed Mechanism for Forming Products 4

Table 1

Optimization Conditions for Forming **4a**^[a]

Entry	Solvent	T/°C	Yield ^[b] /%
1	DMF	90	32
2	HOAc	90	51
3	THF	90	trace
4	H ₂ O	90	trace
5	benzene	90	trace
6	DCM	90	trace
7	EtOH	90	29
8	CH ₃ CN	90	20
9	HOAc	100	60
10	HOAc	120	65
11	HOAc	130	64
12	HOAc	120	77 ^[c]
13	HOAc	120	65 ^[d]

^[a] Reaction conditions: 4-chlorobenzaldehyde (**1a**, 1.0 mmol), 1-(4-nitrophenyl)-2-thiocyanatoethan-1-one (**2a**, 1.0 mmol) and 3-methyl-1-phenyl-1H-pyrazol-5-amine (**3**, 1.0 mmol), solvent (2.0 mL), microwave irradiation, 25 min.

^[b] Isolated yield based on **2a**.

^[c] The mole ratio of **1a**, **2a** and **3** in 1.2:1:1.2.

^[d] Conventional heating, 90 min.

Table 2

Substrate Scope of Bicyclization Reactions under Microwave Heating^[a]

Entry	Product	Ar ²	Time / min	Yield ^[b] / %
1	4a-4j	4a 4-Chlorophenyl	25	77
2		4b 4-Bromophenyl	22	82
3		4c 4-Fluorophenyl	20	81
4		4d 2-Bromophenyl	23	67
5		4e Phenyl	24	76
6		4f 4-Tolyl	25	75
7	4a-4j	4g 3,4,5-Trimethoxyphenyl	28	70
8		4h 2,3-Dimethoxyphenyl	28	58
9		4i 4-Hydroxy-3-methoxyphenyl	27	65
10		4j 4-Bromophenyl	26	69
11		4k 2,4-Dichlorophenyl	26	56
12		4l 3-Nitrophenyl	24	73
13	4j-4m	4m Phenyl	25	60
14		4n 4-Fluorophenyl	23	69
15		4o 4-Chlorophenyl	30	75
16		4p 4-Bromophenyl	28	72
17		4q 4-Nitrophenyl	28	71
18		4r Phenyl	30	65
19	4n-4s	4s 4-Tolyl	30	62

^[a]Reaction conditions: aryl aldehydes (**1**, 1.2 mmol), α-thiocyanate ketones (**2**, 1.0 mmol) and 3-methyl-1-phenyl-1H-pyrazol-5-amine (**3**, 1.2 mmol), HOAc (2.0 mL), 120 °C, microwave irradiation.^[b]Isolated yield based on **2a**.