One-Pot Combinatorial Synthesis of 4-Aryl-1*H*-thiopyrano[3,4-*b*]pyridine-5-one Derivatives

Chang-Sheng Yao, Cui-Hua Wang, Bei Jiang, and Shu-Jiang Tu*

School of Chemistry and Chemical Engineering, Xuzhou Normal University, and Key Laboratory of Biotechnology for Medicinal Plant, Xuzhou, Jiangsu, 221116, P.R. China

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A simple and efficient method for the combinatorial synthesis of highly substituted thiopyrano[3,4-*b*]pyridin-5(4*H*)-one, thiopyrano[3,4-*b*]quinoline-4,6(3*H*,5*H*)-dione, dithiopyrano[3,4-*b*:4′,3′-*e*]pyridine-4,6(1*H*,3*H*)-dione, and pyrazolo[3,4-*b*]thiopyrano[4,3-*e*]pyridin-5(1*H*)-one derivatives has been developed. The synthesis was achieved via one-pot multicomponent reaction of aromatic aldehyde, 2*H*-thiopyran-3,5(4*H*,6*H*)-dione and enamine (such as the derivatives of amine and 1,3-dicarbonyl compounds and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine) in glacial acetic acid. This procedure features short reaction time, generally good to excellent yields, easily available starting materials, and operational simplicity. This chemistry provides an efficient and promising synthetic strategy to diversity-oriented construction of the thiopyrano[3,4-*b*]pyridine skeleton.

Introduction

Multicomponent reactions (MCRs) are one-pot processes in which three or more reactants come together in a single reaction vessel to form a product containing substantial elements of all the reactants.[1] MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the combinatorial chemistry as powerful tools[2] because of their value features such as atom-economy, environmental concerns, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical operation.[3] Therefore, a great deal of current interest is focused on the development of novel MCRs.[4] For example, the most classical synthesis of a 1,4-dihydropyridine (1,4-DHP) is a three-component condensation reaction reported by Hantzsch in 1882.[5] Hantzsch 1,4-dihydropyridines are an important class of drugs for the treatment of cardiovascular diseases such as hypertension and angina pectoris.[6] Thus, in terms of designing and screening new lead compounds, searching for new and facile MCRs to prepare 1,4-DHPs with new functional substituents is highly desirable work.[7]

Thiopyran and fused thiopyran derivatives exhibit various kinds of biological activities, such as weed control[8] and antitumor activity.[9] Pyridines are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products, for example, NAD nucleotides, pyridoxol (vitamin B6), and pyridine alkaloids.[10] Within a long-term research program aiming at the synthesis of novel fused S,N-heterocycles, thiopyranopyridines are of special importance because of their biological activities,[11] such as antitumor,[12] antibacterial, and fungicidal activity,[13] neuroleptic activity,[14] and significant cytotoxicity.[15−18] These examples clearly indicate the remarkable potential of novel thiopyranopyridine derivatives as a source of valuable drug candidates. However, only a few thiopyrano[3,4-*b*]pyridine derivatives were synthesized and their activities as KATP channel openers were reported.[19] Besides, these synthetic methods suffer from long reaction time, multiple steps, high temperature, unsatisfactory yields, and limited diversity. Considering the biological significance of fused S,N-heterocycles, it is valuable to synthesize the compound library based on the important thiopyrano[3,4-*b*]pyridine scaffold with high diversity for biomedical screening. To continue our work on the multicomponent synthesis of heterocyclic compound library with high diversity,[20] herein we report a new, convenient, diversity-oriented, and highly efficient protocol for the synthesis of thiopyrano[3,4-*b*]pyridine collections via one-pot multicomponent reactions under acidic conditions. This method uses readily available raw materials such as aromatic aldehyde, ammonium acetate, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, 1,3-dicarbonyl compounds including ethyl 3-oxobutanoate, methyl 3-oxobutanoate, pentane-2,4-dione, 5,5-dimethylcyclohexane-1,3-dione, and 2*H*-thiopyran-3,5(4*H*,6*H*)-dione.

Results and Discussion

We started by finding optimal conditions for the efficient formation of the thiopyrano[3,4-*b*]pyridines via a one-pot four-component reaction of aromatic aldehyde (**1**), 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**2**), acyclic 1,3-dicarbonyl compounds (**3**), and excess ammonium acetate (Scheme 1). To search for the suitable reaction solvent, the model reaction of 4-bromophenylaldehyde (**1a**, 1 mmol), 2*H*-thiopyran-3,5(4*H*,6*H*)-dione (**2**, 1 mmol), ethyl 3-oxobutanoate (**3a**, 1 mmol), and ammonium acetate (excess) was conducted in CH_3CN, *N*,*N*-dimethylformamide (DMF), ethanol, $CHCl_3$, and glacial acetic acid, (Table 1, entries *1*−*5*) at room temperature, respectively. As shown in Table 1, the reaction in glacial acetic acid (Table 1, entry *5*) exhibits higher yield

* To whom correspondence should be addressed. Phone: 0086-516-83500065. Fax: 0086-516-83500065. E-mail: laotu@xznu.edu.cn.

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Scheme 1. Synthesis of 4-Aryl-1*H*-thiopyrano[3,4-*b*]pyridine Derivatives **4**

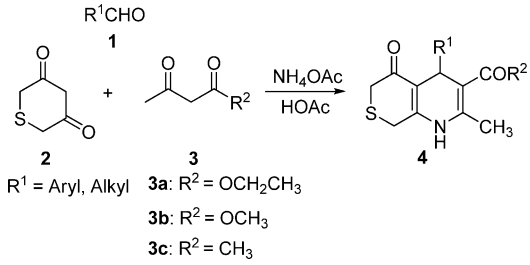


Table 1. Solvent and Temperature Optimization for the Synthesis of **4aa**

entry	solvent	*T* (°C)	time (h)	yield[a] (%)
1	CH_3CN	r.t.	10	73
2	DMF	r.t.	12	80
3	EtOH	r.t.	10	75
4	$CHCl_3$	r.t.	8	50
5	HOAc	r.t.	6	86
6	HOAc	15	10	75
7	HOAc	20	8	78
8	HOAc	40	6	80

[a] Isolated yields.

and greater reaction rate than other counterparts. So glacial acetic acid was used as the solvent to synthesize the desired products.

To further screen for the practical temperature for the synthesis, the previous reaction was carried out in glacial acetic acid at 15 °C, 20 °C, room temperature (25 °C), and 40 °C (Table 1, entries *5*∼*8*), resulting in the isolation of **4aa** in 75%, 78%, 86%, and 80% yields (Table 1, entries *5*∼*8*), respectively. Therefore, room temperature was chosen to synthesize the thiopyrano[3,4-*b*]pyridine derivatives.

Under the conditions described above, a range of valuable structures of ethyl 4,5,6,8-tetrahydro-2-methyl-5-oxo-4-aryl-1*H*-thiopyrano[3,4-*b*]pyridine-3-carboxylate (Table 2, entries *1*−*14*) were synthesized in good to excellent yields within a few hours. As expected, when methyl 3-oxobutanoate (**3b**) and pentane-2,4-dione (**3c**) were used instead of ethyl 3-oxobutanoate (**3a**), the reaction gave the corresponding products in good to excellent yields under the optimized conditions (Scheme 1, Table 2). The structure of **4bb** was identified by IR and ^{1}H NMR and further confirmed by X-ray diffraction analysis (Figure 1).

As shown in Table 2, the effect of electronic nature of the substituents on the aromatic ring did not show strong influence on reaction yields. This protocol can be applied not only to electron-rich and electron-deficient aromatic aldehydes, but also to heteroaromatic aldehydes and aliphatic aldehyde with moderate to excellent yields under the same conditions, which highlighted the wide scope of this condensation.

This sequence is also extended from acyclic 1,3-dicarbonyl compounds to cyclic 1,3-dicarbonyl compounds, such as 5,5-dimethylcyclohexane-1,3-dione (Scheme 2). To expand the scope of amine substrates, ammonium acetate and primary aromatic amines including aniline, *p*-toluidine, and 4-chloroaniline were applied to this protocol. In all cases, the desired reactions took place successfully to afford a series of 5-aryl-1*H*-thiopyrano[3,4-*b*]quinoline-4,6(3*H*,5*H*,7*H*,10*H*)-diones (**6a**-**6s**) in moderate to good yields. The results are summarized in Table 3. The structure of **6k** is confirmed by X-ray diffraction analysis, and its crystal structure is shown in Figure 2.

Actually, 2*H*-thiopyran-3,5(4*H*,6*H*)-dione is a cyclic 1,3-dicarbonyl compound with high reactivty. Setting

Table 2. Synthesis of Compounds **4** in Glacial Acetic Acid without Catalyst

entry	R^1	R^2	time (h)	products	yield[a] (%)	Mp (°C)
1	4-BrC_6H_4 (**1a**)	OEt	6	**4aa**	86	260−261
2	2-FC_6H_4 (**1b**)	OEt	8	**4ab**	84	258−260
3	3-FC_6H_4 (**1c**)	OEt	6	**4ac**	85	250−252
4	4-FC_6H_4 (**1d**)	OEt	7	**4ad**	84	255−257
5	2-ClC_6H_4 (**1e**)	OEt	7	**4ae**	85	224−226
6	3-ClC_6H_4 (**1f**)	OEt	6	**4af**	84	218−220
7	4-ClC_6H_4 (**1g**)	OEt	6	**4ag**	82	274−276
8	2,4-$Cl_2C_6H_3$ (**1h**)	OEt	7	**4ah**	87	251−253
9	3,4-$Cl_2C_6H_3$ (**1i**)	OEt	7	**4ai**	83	245−246
10	3-$NO_2C_6H_4$ (**1j**)	OEt	9	**4aj**	81	237−240
11	3,4,5-$(CH_3O)_3C_6H_2$ (**1l**)	OEt	9	**4ak**	85	194−196
12	4-$(CH_3)_2NC_6H_4$ (**1m**)	OEt	8	**4al**	82	240−242
13	2-Thienyl (**1n**)	OEt	7	**4am**	87	239−240
14	*n*-Propyl (**1o**)	OEt	7	**4an**	84	202−204
15	C_6H_5 (**1p**)	OCH_3	8	**4ba**	81	246−247
16	4-BrC_6H_4 (**1a**)	OCH_3	9	**4bb**	80	216−218
17	2-FC_6H_4 (**1b**)	OCH_3	8	**4bc**	80	251−253
18	3-FC_6H_4 (**1c**)	OCH_3	8	**4bd**	82	245−248
19	2-ClC_6H_4 (**1e**)	OCH_3	9	**4be**	81	207−209
20	4-ClC_6H_4 (**1g**)	OCH_3	9	**4bf**	80	249−252
21	4-$NO_2C_6H_4$ (**1k**)	OCH_3	8	**4bg**	83	220−221
22	3,4,5-$(CH_3O)_3C_6H_2$ (**1l**)	OCH_3	10	**4bh**	84	227−229
23	4-BrC_6H_4 (**1a**)	CH_3	9	**4ca**	81	255−257
24	2-FC_6H_4 (**1b**)	CH_3	8	**4cb**	83	231−233
25	3-FC_6H_4 (**1c**)	CH_3	8	**4cc**	80	227−229
26	2-ClC_6H_4 (**1e**)	CH_3	10	**4cd**	81	237−239
27	3-ClC_6H_4 (**1f**)	CH_3	10	**4ce**	80	249−252
28	4-ClC_6H_4 (**1g**)	CH_3	9	**4cf**	82	242−243
29	3,4-$Cl_2C_6H_3$ (**1i**)	CH_3	10	**4cg**	80	218−220
30	3,4,5-$(CH_3O)_3C_6H_2$ (**1l**)	CH_3	10	**4ch**	81	173−175

[a] Isolated yields.

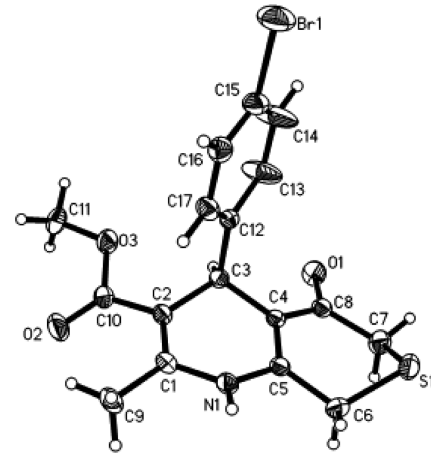


Figure 1. ORTEP drawing of **4bb**.

Scheme 2. Synthesis of 5-Aryl-1*H*-thiopyrano[3,4-*b*]quinoline-4,6(3*H*,5*H*,7*H*,10*H*)-dione Derivatives **6**

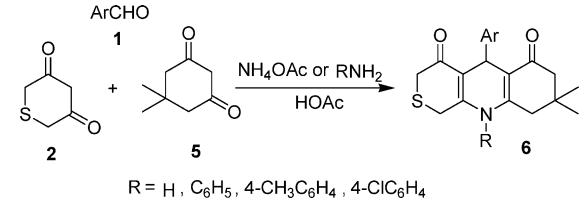


Table 3. Synthesis of Compounds **6** in Glacial Acetic Acid without Catalyst

entry	Ar	R	time (h)	products	yield[a] (%)	Mp (°C)
1	4-BrC_6H_4 (**1a**)	H	13	**6a**	75	265−267
2	4-ClC_6H_4 (**1g**)	H	12	**6b**	72	266−268
3	3-$NO_2C_6H_4$ (**1j**)	H	14	**6c**	70	240−241
4	4-$CH_3C_6H_4$ (**1q**)	H	14	**6d**	75	254−257
5	3-$CH_3OC_6H_4$ (**1r**)	H	13	**6e**	73	228−230
6	4-$CH_3OC_6H_4$ (**1s**)	H	13	**6f**	71	233−235
7	3,4,5-$(CH_3O)_3C_6H_2$ (**1l**)	H	14	**6g**	70	155−157
8	2-Thienyl (**1n**)	H	12	**6h**	74	246−249
9	4-BrC_6H_4(**1a**)	C_6H_5	13	**6i**	80	221−223
10	3-FC_6H_4 (**1c**)	4-$CH_3C_6H_4$	13	**6j**	75	260−261
11	4-ClC_6H_4 (**1g**)	4-$CH_3C_6H_4$	12	**6k**	78	270−271
12	4-FC_6H_4 (**1d**)	4-ClC_6H_4	13	**6l**	74	281−283
13	2-ClC_6H_4 (**1e**)	4-ClC_6H_4	12	**6m**	76	257−259
14	3-ClC_6H_4 (**1f**)	4-ClC_6H_4	14	**6n**	75	248−250
15	3,4-$Cl_2C_6H_3$ (**1i**)	4-ClC_6H_4	13	**6o**	77	239−241
16	3-NO_2-4-OHC_6H_3 (**1t**)	4-ClC_6H_4	12	**6p**	76	262−264
17	4-$CH_3OC_6H_4$ (**1s**)	4-ClC_6H_4	15	**6q**	78	242−244
18	3,4,5-$(CH_3O)_3C_6H_2$ (**1l**)	4-ClC_6H_4	15	**6r**	78	233−235
19	4-$(CH_3)_2NC_6H_4$ (**1m**)	4-ClC_6H_4	14	**6s**	74	226−229

[a] Isolated yields.

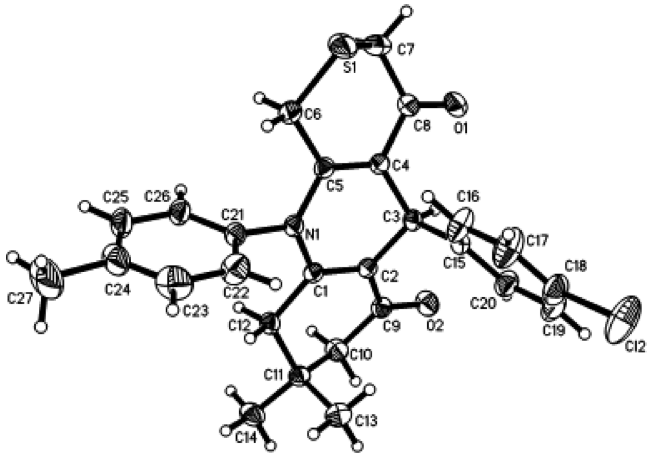
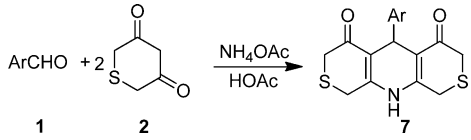


Figure 2. ORTEP drawing of **6k**.

Scheme 3. Synthesis of 5-Aryl-5,7,9,10-tetrahydrodithiopyrano[3,4-*b*:4′,3′-*e*]pyridine-4,6(1*H*,3*H*)-dione Derivatives **7**



molar ratio of 2*H*-thiopyran-3,5(4*H*,6*H*)-dione to aromatic aldehyde at 2:1 means adding another equivalent 1,3-dicarbonyl compound to the reaction system (Scheme 3). So the pseudo four-component reactions were performed in glacial acetic acid at 50 °C and the corresponding dithiopyrano[3,4-*b*;4′,3′-*e*]pyridine products **7** were obtained in good yields (Table 4). These heterocyclic compounds encompass two thiopyranone rings and are known to display a wide range of potential biological activities including antimicrobial, antibacterial, and antifungal activity, KATP activity, and the inhibition of spontaneous bladder contractions.[19]

In our continued study, we performed the reaction of aromatic aldehyde(**1**), 2*H*-thiopyran-3,5(4*H*,6*H*)-dione(**2**), and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine**(8)** under the optimized conditions (Scheme 4). To our pleasure, a series of novel 4-aryl-3-methyl-1-phenyl-4,6,8,9-tetrahydropyrazolo[3,4-*b*]thiopyrano[4,3-*e*]pyridin-5(1*H*)-one derivatives were obtained successfully in high yields at room temperature (Table 5).

Table 4. Synthesis of Compounds **7** in Glacial Acetic Acid without Catalyst

entry	Ar	time (h)	products	yield[a] (%)	Mp (°C)
1	C_6H_5 (**1p**)	8	**7a**	82	>300
2	4-BrC_6H_4 (**1a**)	10	**7b**	85	285−287
3	2-FC_6H_4 (**1b**)	9	**7c**	81	298−300
4	4-FC_6H_4 (**1d**)	10	**7d**	83	272−275
5	4-ClC_6H_4 (**1g**)	9	**7e**	83	251−253
6	3-$CH_3OC_6H_4$ (**1r**)	10	**7f**	85	258−259
7	4-$CH_3OC_6H_4$ (**1s**)	10	**7g**	80	286−289
8	2-Thienyl (**1n**)	9	**7h**	82	>300

[a] Isolated yields.

Scheme 4. Synthesis of 4-Aryl-3-methyl-1-phenyl-4,6,8,9-tetrahydropyrazolo[3,4-*b*]thiopyrano[4,3-*e*]pyridin-5(1*H*)-one Derivatives **9**

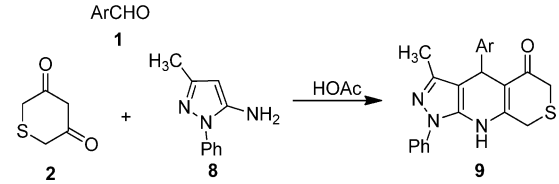


Table 5. Synthesis of Compounds **9** in Glacial Acetic Acid without Catalyst

entry	Ar	time (h)	products	yield[a] (%)	Mp (°C)
1	2-ClC_6H_4 (**1e**)	12	**9a**	86	262−264
2	4-BrC_6H_4 (**1a**)	11	**9b**	82	191−194
3	2-FC_6H_4 (**1b**)	10	**9c**	81	255−257
4	C_6H_5 (**1p**)	12	**9d**	85	233−235
5	3-ClC_6H_4 (**1f**)	14	**9e**	84	215−217
6	4-ClC_6H_4 (**1g**)	12	**9f**	81	178−181
7	4-$CH_3C_6H_4$ (**1q**)	13	**9g**	85	218−221
8	4-$CH_3OC_6H_4$ (**1s**)	15	**9h**	83	211−214
9	3,4,5-$(CH_3O)_3C_6H_2$ (**1l**)	15	**9i**	85	239−241
10	2-Thienyl (**1n**)	13	**9j**	80	226−228

[a] Isolated yields.

The structures of all of the synthesized compounds were characterized by ^{1}H NMR, IR, and HRMS spectra. The structures of **4bb** and **6k** were established by X-ray diffraction analysis further (Figures 1 and 2).

Conclusion

In summary, we have developed a simple and efficient method for the diversity-oriented synthesis of a series of thiopyrano[3,4-*b*]pyridine derivatives via a one-pot multicomponent reaction in acidic media. This procedure features shorter reaction time, generally good to excellent yields, easily available starting materials, and operational simplicity (only one pot).

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4aa**−**4ch**, **6a**−**6s**, **7a**−**7 h**, and **9a**−**9j**, and crystallographic information files (CIF) of **4bb** and **6k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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