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One-Pot Multicomponent Cascade Reaction of *N,S*-Ketene Acetal: Solvent-Free Synthesis of Imidazo-[1,2-*a*]thiochromeno[3,2-*e*]pyridines

Ming Li,* Han Cao, Yong Wang, Xiu-Liang Lv, and Li-Rong Wen*

State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China

liming928@qust.edu.cn; wenlirong@qust.edu.cn

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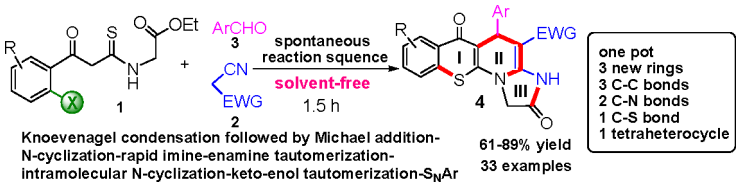
ABSTRACT



Unprecedented imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines have been synthesized via a three-component cascade reaction under solvent-free conditions. This one-pot transformation involving multiple steps and not requiring the use of transition metal catalysts constructs three new C−C bonds, two C−N bonds, one C−S bond, and three new rings with all reactants efficiently utilized.

The solvent-free reaction (SFR)[1] is an important synthetic procedure from the viewpoint of green and sustainable chemistry. Carbon−carbon and carbon−heteroatom bond-forming reactions are central to organic synthesis. Multicomponent reactions (MCRs)[2] involving domino processes are important for generating high levels of diversity giving rise to complex structures by simultaneous formation of two or more bonds from simple substrates. Thus, developing a new, environmentally benign MCR has been recognized as one of the most important topics of green chemistry.[3]

Imidazo[1,2-*a*]pyridine scaffolds represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists that are contained in marketed drugs such as the clinical antiulcer compound soraprazan,[4] the PDE 3 inhibitor olprinone,[5] the sedative zolpidem,[6] and inhibitors of TNF-α expression in T cells.[7] On the other hand, functionalized thiochromones

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represent an important class of heterocycles and have been tested and applied as drugs.[8] Hence, the synthesis of the imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines could be a valuable strategy to discover new bioactive compounds.

Functionalized ketene *S,S*-[9] and *N,S*-acetals[10] have received much attention as versatile building blocks in organic synthesis. Among them, *β*-ketothioamides (KTAs) with general structures **A** and **B** have been proven to be well-known synthons in the construction of heterocyclic systems (Figure 1).[11,12] Ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)acetates **1**, as novel α-oxoketene *N,S*-acetals with seven chemically distinct reactive sites, show intriguing and fascinating structural features and have a different reactivity profile from **A** or **B**. By the special reactivity of ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)acetates **1**, we developed the three-component reactions of **1** with aromatic aldehydes and malononitrile or ethyl 2-cyanoacetate to construct imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridine moiety. In this process, at least nine distinct reactive sites participated, which resulted in the concomitant creation of six new bonds and three new rings. Careful literature search shows that the synthetic application of ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido)-acetates **1** in MCRs has not been disclosed thus far.

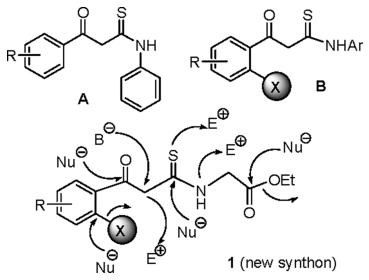
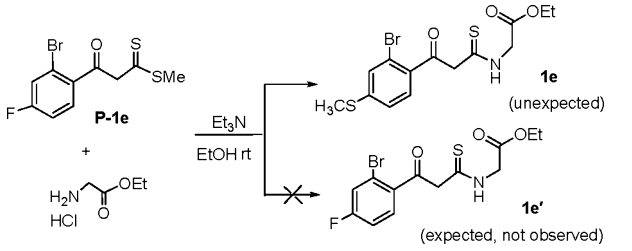


Figure 1. Reactivity profile of KTA.

Ethyl 2-(3-(2-haloaryl)-3-oxopropanethioamido) acetates **1**, required as the key cyclization precursors for the three-component reaction, were readily obtained by the previously reported procedure utilizing *β*-oxodithiocarboxylates with alkyl glycinate hydrochloride in the presence of Et_3N in C_2H_5OH at room temperature.[10e] Surprisingly, when methyl 3-(2-bromo-4-fluorophenyl)-3-oxopropanedithioate was used to react with glycine ethyl ester hydrochloride, ethyl 2-(3-(2-bromo-4-(methylthio)-phenyl)-3-oxopropanethioamido)acetate **1e** rather than **1e′** was obtained, in which a S_NAr reaction of the fluoro atom by the methylthio group took place accidentally (Scheme 1).

Scheme 1. Unexpected Result for Synthesis of **1e**



This unexpected result was also verified by the X-ray diffraction analysis of the product **4bb** (Figure 2). *This unprecedented observation is very rare.*

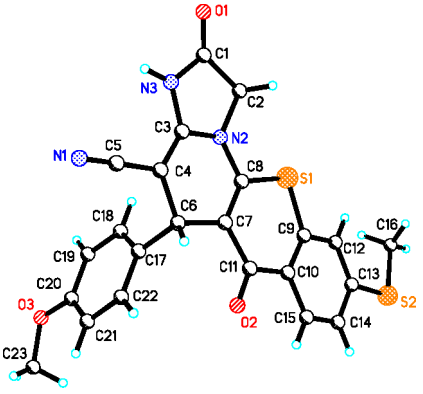


Figure 2. X-ray structure of **4bb**.

Initially, ethyl 2-(3-(2-bromophenyl)-3-oxopropanethioamido)acetate **1a**, malononitrile **2a**, and benzaldehyde **3a** were chosen as the model substrates to optimize reaction conditions including bases, solvents, and reaction temperature (Table 1).

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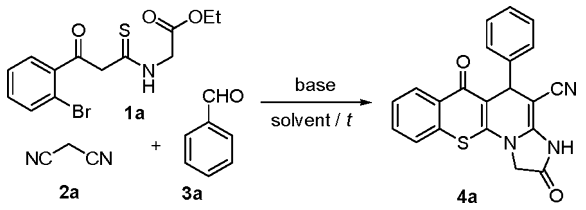
Table 1. Optimization of Reaction Conditions[a]



entry	base (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1		CH_3CN	reflux	6	NR
2	Et_3N (1.0)	CH_3CN	reflux	5	59
3	Et_3N (1.0)	C_2H_5OH	reflux	5	10
4	Et_3N (1.0)	THF	reflux	5	40
5	**Et_3N (1.0)**		**120**	**1.5**	**78**
6	[bmim]OH (1.0)		120	3	30
7	[octmim]OH (1.0)		120	3	45
8	DBU (1.0)		120	3	33
9	DMAP (1.0)		120	3	20
10	Et_3N (0.5)		120	1.5	64
11	Et_3N (1.5)		120	1.5	79
12	Et_3N (1.0)		110	1.5	69
13	Et_3N (1.0)		130	1.5	77

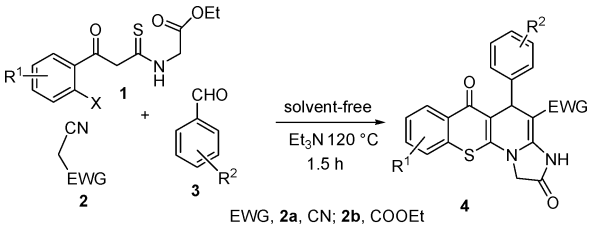
[a] The mixture of **1a** (1.0 mmol), **2a** (1.0 mmol), and **3a** (1.0 mmol) was stirred in a flask in an oil bath. [b] Isolated yield.

No reaction occurred without addition of any base in refluxing CH_3CN for 6 h (entry 1), but when 1.0 equiv of Et_3N was added, the compound 2,6-dioxo-5-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]thiochromeno[3,2-*e*]-pyridine-4-carbonitrile **4a** was obtained in 59% yield (entry 2). Next, different solvents were tested in the presence of Et_3N, but the results were unsatisfactory (entries 3 and 4). To our delight, however, a breakthrough result was achieved when the reaction was carried out under solvent-free conditions at 120 °C; **4a** was formed in good yield of 78%, and the reaction time was shortened to 1.5 h simultaneously (entry 5). Thus, other various bases, such as [bmim]OH, [octmim]OH, DBU, and DMAP, were examined, and the results revealed that they all failed to effectively promote the reactions; instead, the reactions became sluggish and the yields of the corresponding products were lower than with Et_3N (entries 6–9). Next, changing the amount of Et_3N (entries 10 and 11) and changing the reaction temperature (entries 12 and 13) also did not improve the yield of **4a**. It could be concluded that the optimum reaction conditions were solvent-free and Et_3N (1.0 equiv) as the base at 120 °C (entry 5).

To test the generality of this process, the reactions of five different **1a**–**e** with **2a** or **2b** and various aromatic aldehydes **3a**–**m** were examined under the optimized conditions, as shown in Table 2.

All reactions provided good to excellent yields and afforded the corresponding products **4** as a racemic form. For the precursors **1**, aryl bromides showed higher reactivity than aryl chlorides (compare entry 3 with 22, entry 11 with 23 in Table 2). However, for precursors **3** bearing either

Table 2. Synthesis of Compounds **4**



entry	1, X, R^1	2	3, R^2	4	yield[b] (%)
1	**1a**, Br, H	**2a**	**3a,** H	**4a**	78
2	**1a**, Br, H	**2a**	**3b**, 4-F	**4b**	82
3	**1a**, Br, H	**2a**	**3c**, 4-Cl	**4c**	80
4	**1a**, Br, H	**2a**	**3d**, 4-Br	**4d**	79
5	**1a**, Br, H	**2a**	**3e**, 4-CH_3	**4e**	73
6	**1a**, Br, H	**2a**	**3f**, 4-OCH_3	**4f**	71
7	**1a**, Br, H	**2a**	**3g**, 4-NO_2	**4g**	85
8	**1a**, Br, H	**2a**	**3j**, 3-F	**4h**	80
9	**1a**, Br, H	**2a**	**3k**, 3-OCH_3	**4i**	75
10	**1a**, Br, H	**2b**	**3b**, 4-F	**4j**	86
11	**1a**, Br, H	**2b**	**3c**, 4-Cl	**4k**	83
12	**1a**, Br, H	**2b**	**3d**, 4-Br	**4l**	82
13	**1a**, Br, H	**2b**	**3e**, 4-CH_3	**4m**	77
14	**1a**, Br, H	**2b**	**3f**, 4-OCH_3	**4n**	76
15	**1a**, Br, H	**2b**	**3g,** 4-NO_2	**4o**	86
16	**1a**, Br, H	**2b**	**3h**, 2-Cl	**4p**	81
17	**1a**, Br, H	**2b**	**3i**, 3-Cl	**4q**	80
18	**1a**, Br, H	**2b**	**3j**, 3-F	**4r**	83
19	**1a**, Br, H	**2b**	**3l**, 3-Br	**4s**	80
20	**1a**, Br, H	**2b**	**3m**, 2-Br	**4t**	81
21	**1a**, Br, H	**2b**	**3k**, 3-OCH_3	**4u**	78
22	**1b**, Cl, H	**2a**	**3c**, 4-Cl	**4c**	61
23	**1b**, Cl, H	**2b**	**3c**, 4-Cl	**4k**	66
24	**1c**, Cl, 4-Cl	**2a**	**3c**, 4-Cl	**4v**	70
25	**1c**, Cl, 4-Cl	**2b**	**3c**, 4-Cl	**4w**	77
26	**1d**, Cl, 5-Cl	**2a**	**3c**, 4-Cl	**4x**	63
27	**1d**, Cl, 5-Cl	**2b**	**3c**, 4-Cl	**4y**	68
28	**1e**, Br, 4-SMe	**2a**	**3c**, 4-Cl	**4aa**	81
29	**1e**, Br, 4-SMe	**2a**	**3f**, 4-OCH_3	**4bb**	77
30	**1e**, Br, 4-SMe	**2a**	**3g,** 4-NO_2	**4cc**	87
31	**1e**, Br, 4-SMe	**2b**	**3c**, 4-Cl	**4dd**	84
32	**1e**, Br, 4-SMe	**2b**	**3g,** 4-NO_2	**4ee**	89
33	**1e**, Br, 4-SMe	**2b**	**3f**, 4-OCH_3	**4ff**	80

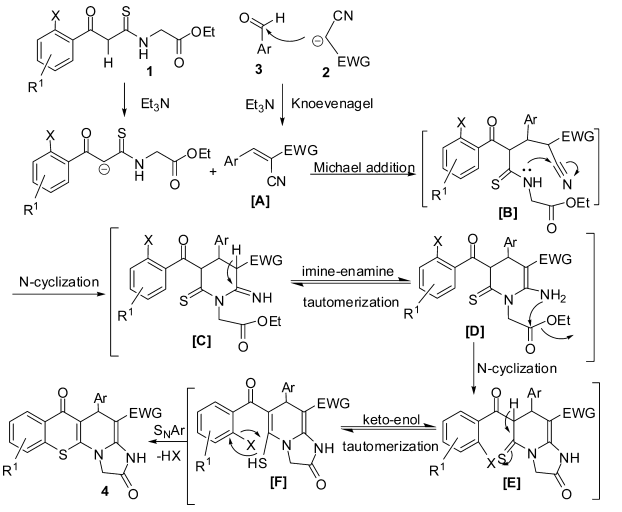
[a] General conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), Et_3N (1.0 mmol), under solvent-free conditions, 120 °C, 1.5 h. [b] Isolated yield after washing by ethanol.

electron-donating or electron-withdrawing substituents, the reactions proceeded very smoothly in all cases.

It is noteworthy that all of the isolated products only need washing with ethanol rather than column chromatography or recrystallization. This easy purification makes this methodology facile, practical, and rapid to execute.

On the basis of the above experimental results, a plausible reaction scenario for the synthesis of imidazo[1,2-*a*]-thiochromeno[3,2-*e*]pyridines is depicted in Scheme 2. First, an aldehyde **3** reacts with an acetonitrile derivative **2** through Knoevenagel condensation by Et_3N catalysis to give intermediate **[A]**; **1** was mediated by Et_3N and deprotonated to form the anion of **1**, which reacts with **[A]**

Scheme 2. Plausible Scenario for the Reaction



through Michael addition to generate the intermediate **[B]**. Then the **[B]** undergoes a *N*-cyclization to give the intermediate **[C]**, which takes place a rapid imine−enamine tautomerization to give **[D]**. Next, the intramolecular *N*-cyclization of **[D]** with losing a molecule of C_2H_5OH leads to the formation of imidazo[1,2-*a*]pyridine motif **[E]** which undergoes keto−enol tautomerization to give **[F]**. Finally, an intramolecular nucleophilic aryl substitution of the *o*-halo of aryl group (S_NAr) by attack of mercapto group leads to imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines **4** with elimination of HX.

In summary, we have successfully developed an efficient one-pot multicomponent cascade to construct imidazo-[1,2-*a*]thiochromeno[3,2-*e*]pyridines via Et_3N-assisted annulations under solvent-free conditions. The process provides an opportunity to avoid the use of transition metal catalysts, toxic solvents and resource consumption. We found that this tandem process involves multiple reactions, including Knoevenagel condensation−Michael addition−*N*-cyclization−rapid imine−enamine tautomerization−intramolecular *N*-cyclization−keto−enol tautomerization−S_NAr sequence. Undoubtedly, this domino synthetic strategy provides a convenient and green way to construct the target molecules in an atom-economic manner. We hope this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

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Supporting Information Available. Experimental and characterization details, ^1H and ^{13}C NMR spectra of **P-1e**, **1e**, and **4**, and crystal data for compounds **4k** and **4bb** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.