Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Direct access to 3-substituted 1,4-oxathiepino[5,6-*b*]pyridine-5-one through one-pot substitution cyclization reaction of 2-mercapto-3-nicotinic acid with α-bromo ketones

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ARTICLE INFO

Article history:
Received 7 October 2013
Revised 4 November 2013
Accepted 8 November 2013
Available online xxxx

Keywords:
One-pot reaction
Cyclization
Multistep reaction
Oxathiepinone

ABSTRACT

A direct, one-pot synthesis route to [1,4]oxathiepino[5,6-*b*]pyridin-5-one derivatives was optimized by reacting different α-bromo ketones with 2-mercaptonicotinic acid. The advantages of this method include high efficiency, regioselective, and multistep conversion in a single-pot protocol. These types of pyridine annulated[1,4]oxathiepin-5-one derivatives are described here for the first time and seem to be interesting candidates for screening purpose. The presented protocol is suitable for using rare chemicals for synthesis of such derivatives.

Introduction

Due to increasing demands for new bioactive molecules for pharmaceutical or agrochemical research, it is of high importance to develop new synthetic routes to drug like molecules which are not yet present in screening libraries.[1,2] Especially heterocyclic structures that have played a vital role in the lead discovery of bioactive molecules of various pharmaceutical interests are important candidates.[1,3] The chemical methods to make drug-like molecules become more valuable when they can facilitate the synthesis of a diverse range of derivatives from simple starting material to provide combinatorial libraries that can be then adapted for automated processing in modern pharmaceutical industry.[4] Here one-pot or serial reagent addition strategies are of advantage because those protocols can be easily and efficiently adapted to synthesis robots omitting demanding separation steps.

The [1,4]-oxathiepin-5-one derivatives of type **2** represent a rare scaffold that was not described in the literature until yet. Unlike structurally analogous thiazepinones, for example, diltiazem, **1** that show a wide range of biological activity, the biological activity of oxathiepinones of type **2** has not been described in the literature. The probable reason could be the lack of efficient synthetic methods that can deliver diversification around these scaffolds. Recently, a few methods appeared in the literature that depicts the synthesis of oxathiepinone derivatives.[5–8] However, these methods are either requiring long reaction time or should be done in a multistep manner.

For the synthesis of 1,4-oxathiepino[5,6-*b*]pyridine-5-one **2**, in this study we used simple starting material 2-mercapto-3-nicotinic acid that possesses thiol and carboxylic acid functional group ortho to each other. Due to the possibility to derive reaction/substitution in various directions the chemistry of this molecule becomes very interesting. It holds a significant importance due to its structural resemblance with 1,4-benzoxathiepinone **3**. A typical synthesis of **3** includes the use of relatively sensitive epoxides and the reaction time required for such derivatives is large.[6] Moreover the selectivity due to ring opening of the epoxide derivatives leads to a mixture of products that make the process inefficient for rapid production of combinatorial libraries.[7]

In this Letter, we designed a facile and straightforward method for the synthesis of analogs of **2**. The most direct method appears to be the reaction of 2-mercapto-3-nicotinic acid with α-bromo ketones and subsequent dehydration that could lead to the bicyclic heterocycle 1,4-oxathiepino[5,6-*b*]pyridine-5-one **2** (Scheme 1). However, to execute this multistep reaction in one pot remains a challenge. To the best of our knowledge, this method for converting 2-mercaptonicotinic acid to 1,4-oxathiepino[5,6-*b*]pyridine-5-one is described for the first time.

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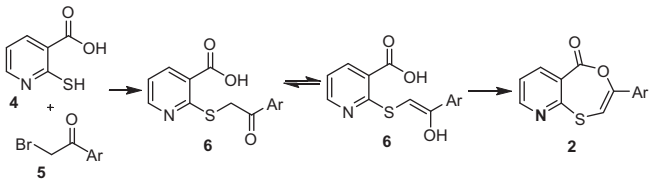
http://dx.doi.org/10.1016/j.tetlet.2013.11.030



Scheme 1. Strategy for the synthesis of 1,4-oxathiepino[5,6-*b*]pyridine-5-one **2**.

Results and discussion

It has been previously reported by us that the S-alkylation of thioamides can be very well executed using either inorganic base like K_2CO_3[9,10] or mild organic bases like Et_3N.[11,12] Under certain circumstances alkyl analog of α-bromo ketone results in thiazole derivatives,[11] while aromatic analogs lead to sulfide contraction products.[9] Unfortunately, the sulfide contraction reaction suffers from relatively poor yields at low temperatures. Here, flow chemistry has played a vital role for overcoming this drawback. Even at intensified process conditions the reaction can be very well controlled by adjusting the flow rates (Fig. 1), temperatures, and pressure in a facile manner.[12]

For optimizing the reaction conditions for selective S-alkylation of 2-mercaptonicotinic acid **4** we have chosen phenacyl bromide **5a** as a model reactant. Initially we examined various solvent systems and bases at 80 °C for 30 min to find the best reaction conditions for S-alkylation (Table 1). Due to the poor solubility of 2-mercaptonicotinic acid in DCM, chloroform, DCE, dioxane, THF, toluene, diethylether, and hexane these solvents were not optimal for testing the optimization. In all of the optimization reactions equimolar amounts of phenacyl bromide were used in order to avoid further alkylation at carboxylic and nitrogen of pyridine that could lead to a mixture of products. The reaction performance under different conditions was investigated by LC–MS analysis. It was observed that the expected sequence of S-alkylation and subsequent lactonization did not proceed under investigated conditions. Instead of getting desired cyclic **2a** we obtained the intermediate **6a** (Scheme 1) as a major product in all the cases. However, it was found that in case of DMSO as solvent and K_2CO_3 as base (Table 1, entry 8), the S-alkylated intermediate **6a** was formed in quantitative yields. DMF, methanol, and ethanol and their combination with bases like Et_3N, K_2CO_3, Na_2CO_3, and pyridine have also furnished this intermediate **6a** in moderate to low yields (Table 1). The desired product **2a** was observed only in trace amounts in some cases. In a comparison between DMSO and DMF as the reaction solvent, DMSO produced the reaction product in considerably short reaction time than DMF. Therefore, we opted for the DMSO as reaction solvent for further experiments.

The optimized reaction conditions for the synthesis of S-alkylated intermediate **6a** (Table 1, entry 8) of course led to clean and high yielding product but the desired cyclization was only in trace amounts. For achieving the cyclization, which is the second step of the sequence, we have screened different reaction times

Table 1
Variation of reaction conditions for the synthesis of 3-phenyl-[1,4]oxathiepino [5,6-*b*]pyridine-5-one **2a**

Entry	Solvent	Base	Yield[a] (%) **6a**	Yield[a] (%) **2a**
1	Methanol	Et_3N	55	Minor
2	Ethanol	Et_3N	45	–
3	DMF	Et_3N	85	–
4	DMSO	Et_3N	87	Minor
5	Methanol	K_2CO_3	85	8
6	Ethanol	K_2CO_3	74	Minor
7	DMF	K_2CO_3	87	Minor
8	DMSO	K_2CO_3	90	6
9	Methanol	Na_2CO_3	78	5
10	Ethanol	Na_2CO_3	65	Minor
11	DMF	Na_2CO_3	89	10
12	DMSO	Na_2CO_3	87	Minor
13	Methanol	Pyridine	35	–
14	Ethanol	Pyridine	40	–
15	DMF	Pyridine	55	–
16	DMSO	Pyridine	62	–
17[b]	DMSO	K_2CO_3	82	Minor
18[c]	DMSO	K_2CO_3	–	90

[a] Isolated yield after 30 min shaking at 80 °C.
[b] The reaction time is 48 h.
[c] 2 equiva of phenacyl bromide was used.

ranging from 30 min to 48 h (Table 1, entry 17) and tuned the reaction temperature from 60 to 120 °C but in no case the desired cyclization was observed. The prolonged reaction time like 48 h at 80 °C rather resulted in partial decomposition of the intermediate. We have also attempted to activate the intramolecular cyclocondensation reaction under thermal intensified flow conditions at 240 °C and 2.5 min residence time. But even this did not serve the purpose. Finally, we found the solutions by converting corresponding carboxylic acid to its analogous ester **7a** (Scheme 2). This was simply achieved by using 2 equiv of phenacyl bromide (**5a**) inside of 1 equiv under similar conditions as described in Table 1 entry 18. Periodic LC–MS analysis of the reaction revealed that the formation of the dialkylated product was achieved within 15 min. Afterward, the cyclization reaction took place and the dialkylated intermediate **7a** has been converted to the cyclic derivative within the following 30 min and furnished the desired **2a**.[13] Additionally, no side product due to alkylation of the pyridine N or thiazole formation has been observed in the LC–MS analysis. Moreover, after acidic workup and extraction with DCM the desired product **2a** gets directly precipitated in acetone. This makes the method simpler because additional chromatographic procedures can be avoided.

In an independent experiment we have isolated the dialkylated product **7a** from the reaction mixture and the pure product was subject to cyclization in DMSO without any base. To our surprise

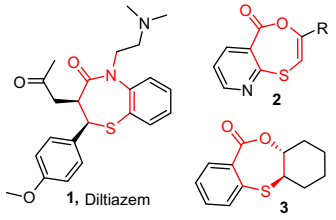
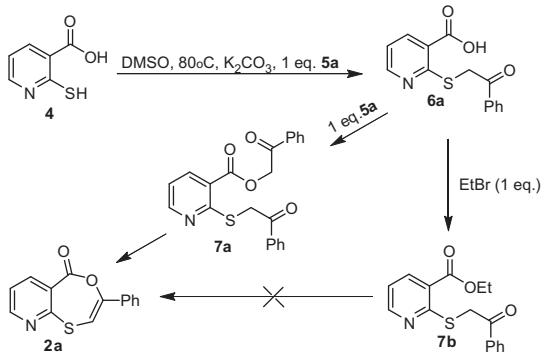


Figure 1. Example structures containing analog of 1,4-oxathiepinone scaffold.



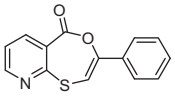
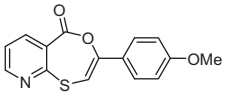
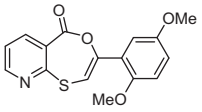
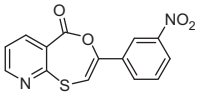
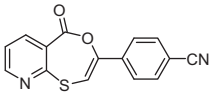
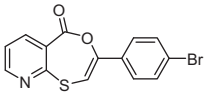
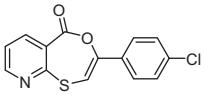
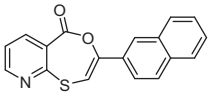
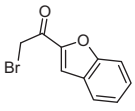
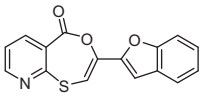
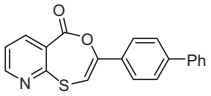
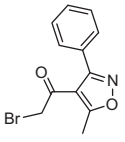
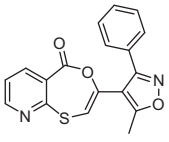
Scheme 2. Influence of ester substitution on conversion of **6a**–**2a**.

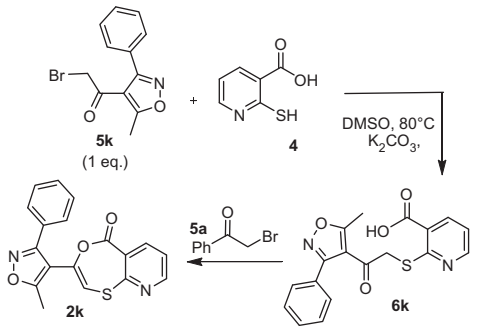
this does not lead to required product **2a**. However upon addition of catalytic amount of K_2CO_3 the required cyclization took place within 5 min. To investigate the role of the ester moiety for the cyclization reaction (Scheme 2) the ethyl ester **7b** was prepared. In this case 1 equiv of α-bromo ketone was introduced under same set of conditions to receive S-alkylated intermediate **6a**. After complete consumption of starting material **4**, 1 equiv of ethyl bromide was added to the reaction mixture to form ethyl ester **7b**. Interestingly, ethyl ester derivative **7b** was obtained but no further cyclocondensation to derivative **2a** was observed after 2 h of heating at 80 °C. However, after a prolonged heating of 24 h a partial conversion to cyclic derivative **2a** was observed. This experiment has concluded that the esterification with bromo ketones **5a** results in the phenylethyl-2-one group which can act as a good leaving group during intramolecular cyclocondensation (Scheme 2).

The observed reactions revealed the sequential alkylation of the sulfur and the carboxylic acid groups by the α-bromo ketone and the subsequent cyclization. Therefore the S-bound z-enolate acts as the nucleophile in an intramolecular substitution reaction and by removing the ester fragment provides desired cyclic lactone **2a**.

To explore the scope of this reaction protocol various new derivatives were prepared by altering the substituents of the α-bromo ketones. Initially, we have tested the influence of electron donating substituents like methoxy on the reaction performance. Use of *p*-methoxyphenyl-1-bromo-2-ethanone **5b** yields the desired product **2b** in 78%. A 2,5-dimethoxyphenyl-1-bromo-2-ethanone **5c** furnishes required product **2c** in 84% yield. Electron donating substituents seem to have no influence on the reaction performance and furnishe the desired products in quantitative yields. On the other hand strongly electron withdrawing substituents like NO_2 and CN were tested for their performance and yielded desired products **2d** and **2e** in 92% and 94% isolated yields. Monitoring the reaction kinetics by LC–MS analysis has shown that the desired product was formed in relatively short reaction time as compared to the reaction where the unsubstituted phenyl derivative of α-bromo ketone was used. However, halogen substitutions

Table 2
1,4-Oxathiepino[5,6-*b*]pyridine-5-one derivatives

Entry	α-Bromo ketone **5**	Product **2**	Isolated yield (%)
a	$PhCOCH_2Br$		90
b	$4\text{-}OMeC_6H_3COCH_2Br$		78
c	$2,5\text{-}(OMe)_2C_6H_3COCH_2Br$		84
d	$3\text{-}NO_2C_6H_4COCH_2Br$		92
e	$4\text{-}CNC_6H_4CH_2Br$		94
f	$4\text{-}BrC_6H_4COCH_2Br$		88
g	$4\text{-}ClC_6H_4COCH_2Br$		90
h	$\beta\text{-}C_{10}H_7COCH_2Br$		87
i			76
j	$4\text{-}PhC_6H_4COCH_2Br$		85
k			76



Scheme 3. Synthesis of **2k**.

like *p*-bromo **5f**, and *p*-chloro **5g** derivatives have shown similar reactivity compared to unsubstituted or electron donating substituents and furnished products in 88% and 90% yields, respectively. Furthermore we made use of β-naphthyl **5h**, benzofuran **5i**, and *p*-phenyl **5j** derivatives of α-bromo ketones. All have furnished the required products **2h**, **2i**, and **2j** in 87%, 76%, and 85% yields, respectively.

As discussed above the method is based on the use of two equivalents of α-bromo ketones that may become a disadvantage when rare or expensive α-bromo ketone derivatives are necessary. We used the expensive α-bromo ketone **5k** (Table 2) as reactant to receive more complex derivatives of type **2k** (Table 2 and Scheme 3). In analogy to the observation from the reaction optimization the use of equivalent quantities of both reactants (**4** and **5k**) did not furnish cyclization product at all. Only the mono substituted S-alkylated derivative was obtained. In order to overcome this problem, we have introduced another equivalent of abundantly available phenacyl bromide **5a** to the reaction mixture to make ester of carboxylic acid and subsequent cyclization (Scheme 3). As expected this strategy has smoothly furnished the required cyclic derivative **2k** in 76% yields. By using this method atom economy, with respect to rare α-bromo ketone derivatives, has been significantly improved and the useful multistep single-pot method has been introduced that is suitable for using rare chemicals.

Conclusions

In summary, we have described an unprecedented and efficient method for the synthesis of 1,4-oxathiepino[5,6-*b*]pyridine-5-one derivatives from 2-mercaptonicotinic acid. The reaction proceeds as stepwise alkylation with α-bromo ketones, first on sulfur then carboxylic acid and continues in a cyclization reaction. This one-pot methodology permits the use of a wide variety of α-bromo ketones. For rare starting materials an alternative economical method to save expensive building blocks has been introduced too. The capability of a straightforward method was proven by the preparation of 11 different derivatives of 1,4-oxathiepino[5,6-*b*]pyridine-5-one.

Acknowledgments

This work has been supported by the German Federal Ministry of Education and Research and the Thuringian Ministry of Culture (FKZ03ZIK062, FKZ03ZIK465, OPTIMI I FKZ 16SV3701 OPTIMI II, BMBF FKZ 16SV5473 and Nanozellkulturen, TMK/TMWAI FKZ B714-09064) within the Initiative 'Centre for Innovation Competence', MacroNano®, the AIF FKZ: KF2731201MDO, Carl Zeiss Stiftung 0563-2.8/399/1, WK Basis FKZ: 03WKCB010 and European Commission under FP7 ICT FET OPEN (FKZ 296590). We thank Katrin Risch and Dr. Eric Täuscher for measuring the NMR and IR and CHNS data.

Supplementary data

Supplementary data (experimental procedures, characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.030.

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13. *Representative procedure:* A 4-mL screw capped reaction vial was charged successively with 2-mercaptonicotinic acid (100 mg, 0.65 mmol), phenacyl bromide (256 mg, 1.30 mmol) and potassium carbonate (180 mg, 1.30 mmol) in 2 ml DMSO. The solution was shaked at 80 °C for 1 h. Complete disappearance of 2-mercaptonicotinic acid in LCMS confirms the completion of reaction. Upon completion of the reaction, the mixture was quenched with few drops of conc. HCl and 10 mL water. The mixture was extracted with DCM (3 × 10 mL), and the combined extract was dried with sodium sulfate and concentrated. The solid product obtained after the evaporation of solvent was further purified by filtration and washing with acetone. The combined yield of the isolated product **2a** was 90%.