Tetrahedron Letters 50 (2009) 2094–2096

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Novel and efficient synthesis of 4-sulfonyl-2-pyridones

Martha L. Minich [a,*], Isa D. Watson [b], Kevin J. Filipski [a], Jeffrey A. Pfefferkorn [a]

[a] Pfizer Global Research and Development, Groton Laboratories, Groton, CT 06340, USA
[b] Department of Chemistry, Hampton University, Hampton, VA 23668, USA

ARTICLE INFO

Article history:
Received 13 December 2008
Revised 13 February 2009
Accepted 16 February 2009
Available online 21 February 2009

ABSTRACT

Heterocyclic 4-sulfonyl-2-pyridones represent useful scaffolds for drug discovery and are also versatile synthetic building blocks. Herein we describe a novel and efficient synthesis of this heterocyclic ring system utilizing an acid mediated cyclo-condensation reaction. This synthetic method affords convenient access to structurally diverse N-substituted 4-sulfonyl-2-pyridones in moderate to good yields.

Substituted 2-pyridones represent useful scaffolds for drug discovery and are also versatile synthetic building blocks. During a recent medicinal chemistry program, we required efficient synthetic access to diversely substituted 4-sulfonyl-2-pyridones (**1**). As shown in Figure 1, such heterocycles have found applications in a variety of therapeutic areas, including: NHE-3 inhibitors (**2**), angiotensin II receptor antagonists (**3**), glucokinase activators (**4**), CB2 agonists (**5**) and thrombin inhibitors (**6**).[1a–e] Additionally, 4-sulfonyl-2-pyridones have also been utilized as synthetic intermediates in a variety of cycloaddition reactions.[2]

There are several methods available for the synthesis of N-substituted-4-sulfonyl-2-pyridones (**1**); however, these existing methods have shortcomings that limit their synthetic utility. The first method involves the N-alkylation or N-arylation of 2-pyridones (available from the corresponding 2-alkoxy- or 2-halo-pyridine precursor).[3] This method generally suffers from a lack of *N*- versus *O*-selectivity and its diversity is limited by the availability of suitable functionalized pyridines. A second synthetic method involves condensation of amines with substituted pyrones to generate the corresponding pyridones.[4] While this second method resolves the *N*- versus *O*-regioselectivity problem associated with the alkylation approach, it is similarly limited by the availability of diversely functionalized pyrone precursors.

In light of these limitations, we sought to develop a novel method for the efficient synthesis of 4-sulfonyl-2-pyridones that would enable the incorporation of diversity at both the sulfonyl and nitrogen positions. As shown in Scheme 1, we retrosynthetically anticipated that the issue of *N*- versus *O*-selectivity associated with previous synthetic methods could be resolved via reaction of diversely functionalized primary amines (R_3NH_2) with a polyfunctionalized linear precursor such as **9** bearing a carboxylic acid at one terminus and a masked aldehyde at the other. In a forward sense, it was envisaged that after an initial amidation event to generate **8**, subsequent treatment of this amide with acid would reveal a terminal aldehyde **7** that would undergo spontaneous condensation with the nitrogen of the terminal amide resulting in ring closure followed by dehydration to generate the desired 4-sulfonyl-2-pyridone (**1**).[5] As illustrated, the intermediate **9** required for this cyclo-condensation strategy could be prepared via oxidation of the corresponding sulfide **10** which itself was accessible from 1,3-diketone derivatives such as **11** via activation as an enol

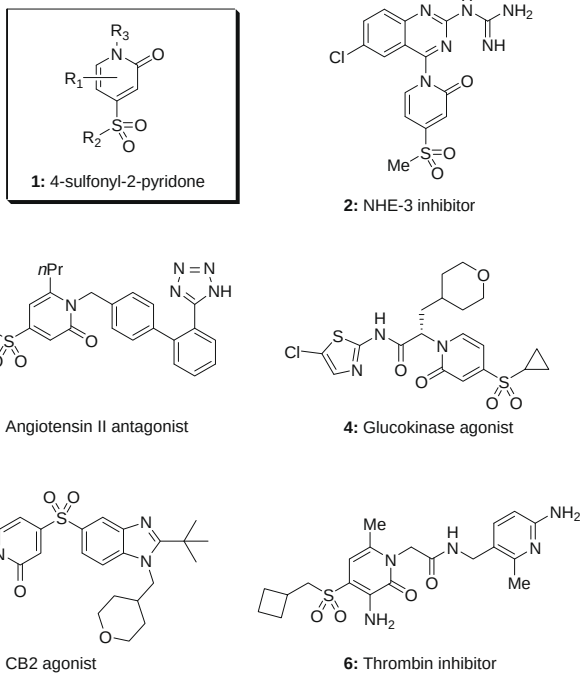

Figure 1. Representative examples of 4-sulfonyl-2-pyridones.

* Corresponding author.
E-mail address: martha.l.minich@pfizer.com (M.L. Minich).

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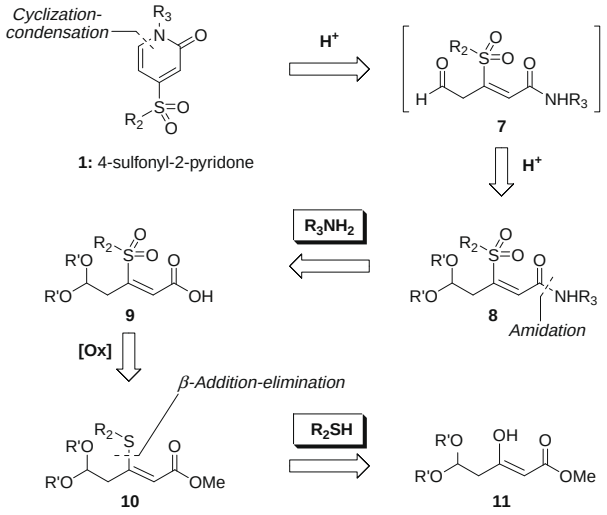
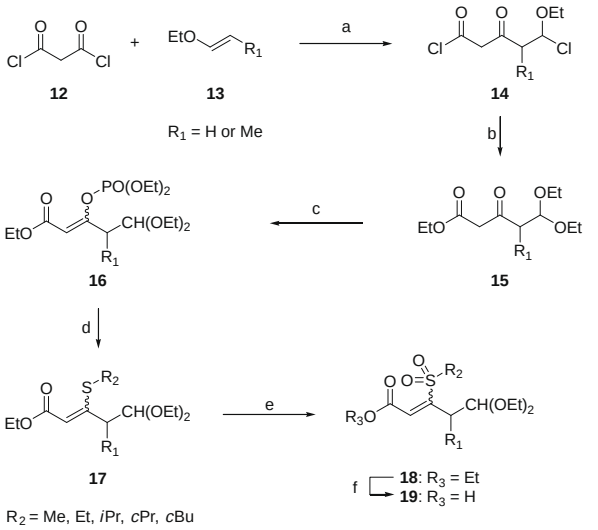
doi:10.1016/j.tetlet.2009.02.120



Scheme 1. Retrosynthetic analysis of 4-sulfonyl-2-pyridones.

phosphonate followed by β-addition-elimination with diversely substituted thiols (R_2SH) and a suitable base.

As outlined in Scheme 2, the synthesis of various cyclization precursors commenced with reaction of malonyl chloride (**12**) with vinyl ethers **13** to form intermediate **14** which was subsequently treated with ethanol followed by triethylamine (caution: exothermic reaction) to generate ketoester **15**. Ketoester **15** could alternatively be prepared through the same sequence except starting with the corresponding monoester acid chloride (e.g., ethyl 3-chloro-3-oxopropionate), however, the addition reaction on this substrate requires higher reaction temperatures along with longer reaction times and proceeds in lower yields relative to the more reactive malonyl chloride.[6] The enolate of ketoester **15** was then generated by treatment with sodium hydride and reacted with diethyl chlorophosphate to afford enol phosphate **16** as an inconsequential mixture of geometric isomers.[7] The introduction of diversely substituted thiols was accomplished through a β-addition–elimination reaction.[8] In this event, the requisite thiolate anion was generated with sodium hydride and then added to enol phosphate **16** to afford sulfide **17**. Reaction optimization studies revealed that to achieve high yields in this reaction, a residual amount of the starting thiol was required, which presumably functioned as a proton source to catalyze the reaction. Based upon this observation, these reactions were typically run with sub-stoichiometric base relative to the starting thiol. The requisite thiol starting materials were either purchased (methanethiol, ethanethiol and isopropanethiol) or synthesized (cyclobutanethiol and cyclopropanethiol). Those requiring synthesis were prepared in 38–45% yields as ethereal solutions from the respective alkyl bromides by generation of the Grignard reagents followed by addition of elemental sulfur and subsequent reduction with lithium aluminium hydride.[9] In the case of methanethiol, since this reagent is only conveniently available as a salt, these addition reactions required the addition of 0.2–0.3 equiv. of ammonium chloride to serve as a proton source.

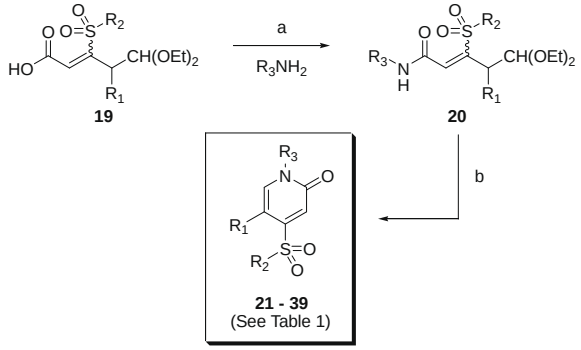


Scheme 2. Synthesis of cyclization precursors. Reagents and conditions: (a) Et_2O, 0 °C, 1 h; (b) (i) EtOH, 0–5 °C; (ii) Et_3N, 10–25 °C, 0.5 h, 60–80% over two steps; (c) (i) NaH, THF, 0 °C, 10 min; (ii) $(EtO)_2POCl$, THF, 12 h, 55–70%; (d) (i) NaH, R_2SH, THF, −60 to 25 °C or R_2SNa, NH_4Cl, THF, −60 to 25 °C, 12 h, 75–90%; (e) *m*CPBA, CH_2Cl_2, 0–25 °C, 1 h, 90–100%; (f) LiOH, MeOH, THF, H_2O, 25 °C, 0.5 h, 50–100%.

With the sulfide **17** in hand, oxidation with *m*CPBA afforded smooth conversion to the corresponding sulfone **18**. Finally, the ester of **18** was saponified to carboxylic acid **19** prior to pyridone ring formation.

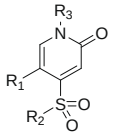
As outlined in Scheme 3, the scope of this heterocycle forming reaction was then evaluated by initially coupling carboxylic acid **19** to a series of diversely substituted amines using PyBrOP® and Hunig's base to produce amides **20**. PyBrop® was selected as the coupling agent for this amidation to minimize the epimerization risk for chiral amines (e.g., **29**, **33**–**39**); however, other coupling reagents were also equally effective in this transformation. Once prepared, the resultant amides were then treated with aqueous 1 N HCl in THF and heated to reflux resulting in cyclization to generate the desired 4-sulfonyl-2-pyridones (**21**–**39**, Table 1). Examination of the results summarized in Table 1 revealed that this cyclization reaction worked well for most aliphatic amides, including alkyl amides (**21**–**24**), benzyl amides (**26**–**29**) and amido acid esters (**32**–**39**). Encouragingly, in the case of chiral amido acid esters (**33**–**39**), the stereochemical integrity of the starting amine was preserved in the products. Amides that tended to not perform well in the cyclization reaction were anilides (**30**–**31**) or amides bearing additional reactive functionality such as hydroxyethanolamide **25**.

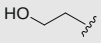
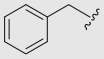
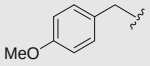
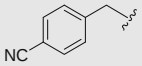
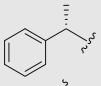
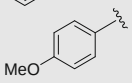
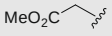
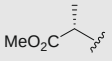
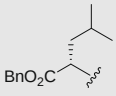
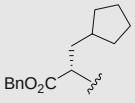
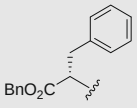
In conclusion we have described a novel method for the synthesis of diversely functionalized 4-sulfonyl-2-pyridones using an acid-mediated cyclo-condensation reaction. This synthetic method affords convenient access to structurally diverse N-substituted 4-sulfonyl-2-pyridones in moderate to good yields.



Scheme 3. Synthesis of 4-sulfonyl-2-pyridones. Reagents and conditions: (a) PyBrOP®, DIPEA, CH_2Cl_2, 0–25 °C, 12 h; (b) THF, HCl (aq), 60–80 °C, see Table 1 for yields.

Table 1
Products and yields of pyridone cyclization reactions



	R_1	R_2	R_3	Yield[a] (%)
21	H	Me	Et	70
22	H	Me	*n*Pr	68
23	H	Me	*i*Pr	59
24	H	Me		82
25	H	Me		9
26	H	Me		37
27	H	Me		74
28	H	Me		46
29	H	Me		51
30	H	Me		27
31	H	Me		22
32	H	Me		58
33	H	Me		43
34	H	Me		60
35	Me	Et		42
36	H	*i*Pr		78
37	H	*c*Bu		58
38	H	*c*Pr		53
39	H	*i*Pr		58

[a] Isolated yields of chromatographically pure (>95%) products.

Acknowledgments

We would like to thank Stephen W. Wright for valuable mechanistic discussions, Daniel E. Virtue for chiral analysis support and Matthew S. Teague for mass spectrometry analysis.

Supplementary data

Experimental procedures and spectral data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.120.

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