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Novel Approach for the Synthesis of Five-Membered-Ring-Fused Pyrazinones

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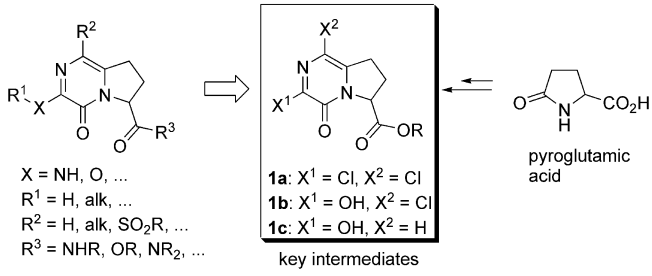
We describe a new route to access important pharmaceutical intermediates for the synthesis of constrained fused pyrazinones. These compounds are prepared in five to seven steps with a good overall yield from glycine methyl ester and commercial propanediol derivatives involving an intramolecular alkylation of a glycine moiety as key step.

Introduction

Serine proteases are an important class of enzymes.[1] Indeed, in mammals, these peptidases perform many important functions, particularly in digestion, blood clotting, immune system and inflammation. They are consequently involved in the processes of diverse diseases (thrombosis, cardiovascular disease, HCV infection etc.). That is the reason why it is important to modulate the activity of these enzymes. During the last 30 years, peptidomimetic molecules are taking an important part in medicinal chemistry.[2] In this field of research, compounds containing a pyrazinone moiety were widely studied due to their potential biological activity, in particular as serine protease inhibitor.[3] More precisely, the pharmaceutical industry has focused the attention on the use of conformationally constrained peptide analogues as serine protease inhibitors.[4] Then, diversely substituted amino-fused pyrazinones were described as thrombin,[4e] prolyl oligopeptidase[4f] or HCV NS3 protease inhibitors.[4g] In all cases, the key intermediates for the preparation of these fused compounds are pyrazinones **1a**–**c** (Scheme 1).

Until now, these fused intermediates were prepared in seven steps from pyroglutamic acid in an overall yield of 22%.[4e] However, reduction and cyanation steps proceeded at very low temperature, and some reactions are difficult to be reproduced on a larger scale, thus limiting seriously the further development of this route. For these reasons, we have focused our attention on a new route for the preparation of these pyrazinones **1** involving a Strecker reaction and an intramolecular alkylation as key steps. In this paper, we report a novel approach for a rapid and efficient synthesis of these intermediates.



Scheme 1. Structures of key intermediates.

Results and Discussion

Our retrosynthetic strategy employs as key step an intramolecular alkylation of the glycine moiety of the pyrazinone **2** (Scheme 2). This product is prepared from the amino nitrile **3** through a classical cyclocondensation step with oxalyl chloride.[5] The amino nitrile **3** would be obtained by a modified Strecker reaction between the readily available glycine methyl ester and the aldehyde **4** derived from propanediol.

Our synthesis began with a modified Strecker reaction of glycine methyl ester and the propanediol derivative **4** obtained by a Swern oxidation of the commercial monoprotected propanediol (Scheme 3). The amino nitrile **3** was isolated in good yield by the addition of TMSCN in the presence of $ZnCl_2$ in MeOH at –15 °C.[6] Then, the intermediate pyrazinone **5** was synthesized by treatment of **3** with oxalyl chloride in DCM in the presence of a catalytic amount of DMF.[7] Selective debenzylation of **5** by treatment with $AlCl_3$ in DCM gave the alcohol **6** in 90% yield. This compound was treated with thionyl chloride or mesyl chloride

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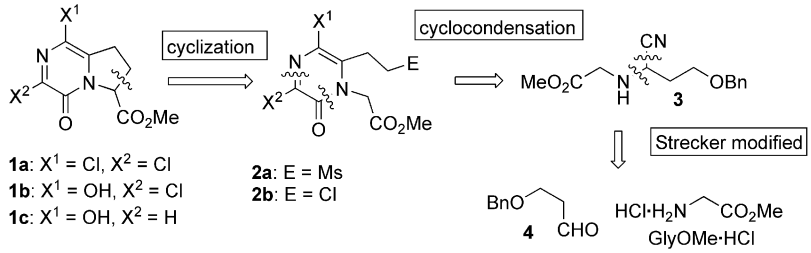
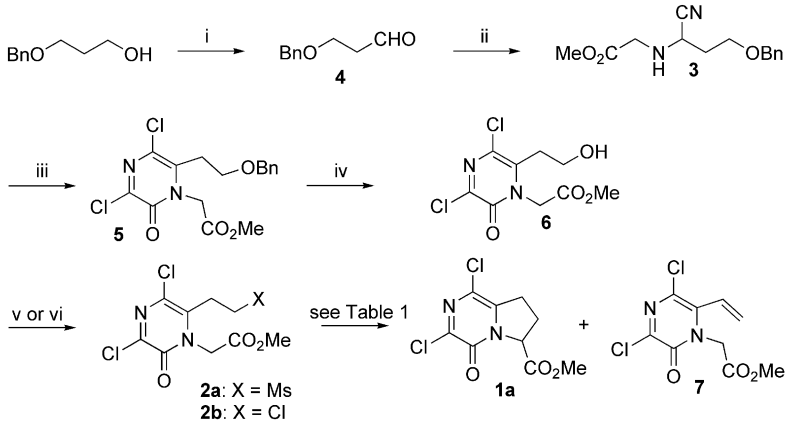


Scheme 2. Retrosynthetic analysis.



Scheme 3. Reagents and conditions: (i) Swern conditions, 85%; (ii) GlyOMe·HCl, NEt_3, $ZnCl_2$, room temp., then TMSCN, –15 °C to room temp., 85%; (iii) oxalyl chloride, DCM, room temp., then cat. DMF, 60%; (iv) $AlCl_3$, DCM, room temp., 90%; (v) $SOCl_2$, DCM, cat. DMF, reflux, 80%; (vi) mesyl chloride, NEt_3, DCM, 82%.

to give the chlorinated product **2b** or the mesylate **2a** in 80% or 82% yield, respectively. With these products in hand, the intramolecular alkylation of the mesylate **2a** to the desired fused compound **1a** was investigated next. A variety of basic conditions were examined to realize this transformation (Table 1).

Table 1. Intramolecular alkylation of pyrazinones **2a**,**b**.

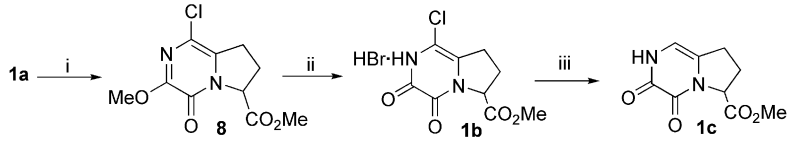
Entry	X	Reagent (equiv.)	Solvent, *T* [°C]	Yield of **1a/7**[a]
1	Ms	LDA (1)	THF, –78	28:27
2	Ms	LDA (2)	toluene, –78 to r.t.	0:0[b]
3	Ms	NaH (1)	THF, reflux	40:40
4	Ms	NaH (1)	DMF, r.t.	[c]
5	Ms	LiTMP (1)	THF, –78	22:18
6	Ms	DBU (1)	acetonitrile, 0	0:100
7	Ms	*t*BuOK (4)	THF, 0	15:0
8	Ms	*t*BuOK (4)	toluene, 0	51:10
9	Ms	*t*BuOLi (4)	THF, 0	19:0
10	Ms	*t*BuOLi (1)	toluene, 0	29:6
11	Ms	NaOH (2)/TBAB (0.1)	toluene, 0	0:100
12	Ms	LiHMDS (2)	toluene, –78 to r.t.	31:30
13	Ms	KHMDS (2)	toluene, –78 to r.t.	0:0[b]
14	Ms	KHMDS (2)	THF, –15	60:0
15	Cl	KHMDS (2)	THF, –15	70:0

[a] Isolated yield. [b] No reaction. [c] Degradation of starting material.

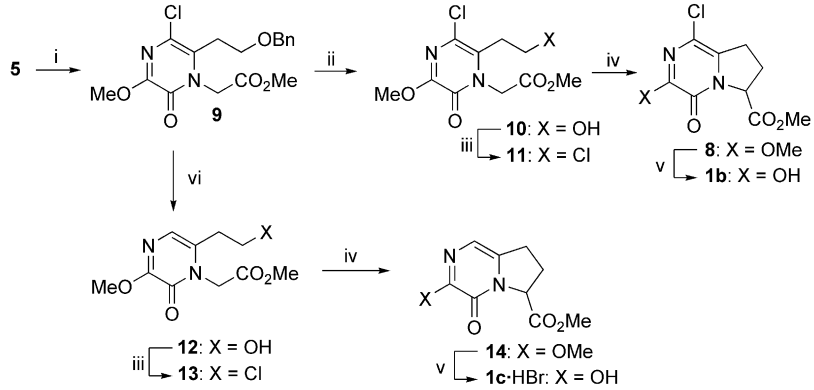
When lithium amide bases (LDA, LiTMP, LiHMDS) were used, no selectivity was observed, and an equimolar mixture of **1a/7** was obtained in moderate yields (Entries 1, 5, 12). A similar result was noted in the presence of sodium hydride in THF (Entry 3). No reaction was observed with LDA or KHMDS in toluene at low temperature (Entries 2, 13). In the presence of DBU or under phase-transfer conditions, only the elimination product **7** was obtained (Entries 6, 11). The use of potassium *tert*-butoxide (Entries 7, 8) or lithium *tert*-butoxide (Entries 9, 10) gave poor results, most likely due to the formation of by-products arising from transesterification and substitution of the chlorine atom at the C-3 position. We finally found that the reaction proceeds most efficiently when KHMDS was added to a solution of compound **2a** in THF at –15 °C (Entry 12). Under these conditions, the substrate was totally consumed, and the desired product **1a** was isolated in a moderate yield of 60%. However, this reaction could be significantly improved up to 70% yield by using the chlorinated product **2b** (Entry 13).

The introduction of a methoxy group at the C-3 position was carried out in the presence of sodium methoxide in MeOH (Scheme 4). Then, the *O*-demethylation was achieved by heating **8** under strong acidic conditions (HBr in acetic acid) providing the desired product **1b** in a quantitative yield. Finally, the dechlorination was performed by hydrogenation in the presence of Pd/C and triethylamine to furnish **1c**.

Alternatively, the cyclization step could also be accomplished on pyrazinones **11** and **13**, these last two being obtained from dichloropyrazinone **5**. After treatment of dichloropyrazinone **5** with sodium methoxide, selective nucleophilic substitution occurred at C-3 to give rise to pyrazinone **9** in 85% yield. Selective debenzylation was achieved



Scheme 4. Reagents and conditions: (i) MeONa, MeOH, room temp., 91%; (ii) 33% HBr in acetic acid, 40 °C, quant.; (iii) H_2, Pd/C, NEt_3, EtOAc, quant.



Scheme 5. Reagents and conditions: (i) MeONa, MeOH, room temp., 85%; (ii) H_2, Pd/C, MeOH, 85%; (iii) $SOCl_2$, DCM, cat. DMF, reflux, 82% from **10**, 54% from **12**; (iv) KHMDS, THF, –15 °C, 70% for both; (v) 33% HBr in acetic acid, 40 °C, quant. for both; (vi) H_2, Pd/C, EtOAc, then NEt_3, 91%.

by conducting the hydrogenation step in the presence of Pd/C in methanol to afford pyrazinone **10** in 85% yield. In contrast, both dechlorination and debenzylation occurred smoothly when pyrazinone **9** was subjected to hydrogenation in EtOAc in the presence of triethylamine to furnish compound **12** in 91% yield. After chlorination of alcohols **9** and **12**, the resulting pyrazinones **11** and **13** (isolated in 82% and 54% yield, respectively) were subjected to cyclization under the conditions previously optimized. In both cases, the desired fused pyrazinones **1b** and **1c** were obtained in 70% yield (Scheme 5).

Conclusions

We have accomplished an efficient and short synthesis of these key intermediates by five-membered-ring fusion from readily available starting materials. The application of this route for the enantioselective synthesis of these compounds is currently underway.

Experimental Section

Typical Experimental Procedure for the Intramolecular Alkylation: A solution of KHMDS (0.5 M in toluene, 4 mL, 2 equiv.) was added dropwise to a solution of **2b** (0.30 g, 1 mmol) in THF (10 mL) at –15 °C. The temperature was slowly (1.5 h) raised to 0 °C, and the mixture was hydrolyzed at this temperature by addition of a saturated aqueous solution of NH_4Cl (10 mL), and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (EtOAc) gave pyrazinone **1a** as a pale yellow oil (0.185 g, 70%). R_f = 0.34 (EtOAc/cyclohexane, 3:1). IR (KBr): $\tilde{\nu}$ = 2925, 1739, 1674, 1593, 1370, 1226, 1150, 1075, 793 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C, 300 MHz): δ = 5.17 (dd, $^3J_{H\text{-}H}$ = 9.6, $^3J_{H\text{-}H}$ = 3.0 Hz, 1 H, C*H*CH_2), 3.82 (s, 3 H, CH_3), 3.22–3.15 (m, 2 H, C$H_2$$CH_2$CH), 2.66–2.38 (m, 2 H, CH_2CH) ppm. ^{13}C NMR ($CDCl_3$, 75MHz): δ = 168.9 (C), 151.4 (C), 144.3 (C), 140.5 (C), 119.8 (C), 63.7 (CH), 53.8 (CH_3), 29.6 (CH_2), 26.6 (CH_2) ppm. MS (EI): *m*/*z* (%) = 264 (20) $[M + H]^{+\cdot}$, 262 (32), 204 (90), 202 (100), 175 (62). $C_9H_8Cl_2N_2O_3$ (263.08): calcd. C 41.09, H 3.07, N 10.65; found C 40.91, H 3.01, N 10.59.

Supporting Information (see footnote on the first page of this article): Complete description of all of the experimental procedures as well as the characterization of all new compounds.

Acknowledgments

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