Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 5063–5067

Synthesis of the 2*H*-quinolizin-2-one scaffold via a stepwise acylation—intramolecular annulation strategy

Swaminathan R. Natarajan,[a,*] Meng-Hsin Chen,[a,*] Stephen T. Heller,[a] Robert M. Tynebor,[a] Ellen M. Crawford,[a] Cui Minxiang,[b] Han Kaizheng,[b] Jingchao Dong,[b] Bin Hu,[b] Wu Hao[b] and Shu-Hui Chen[b]

[a]*Departments of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Chemistry, WuXi Pharmatech, Bldg 1, #288FUTE Zhonglu, Waigaoqiao TZ, Shanghai 200131, China*

Received 13 May 2006; accepted 15 May 2006

Abstract—A rapid entry into the 2*H*-quinolizin-2-one starting from 2-alkyl pyridine has been developed. Initial deprotonation of a 2-alkyl pyridine followed by acylation with a β-TMS-propyonate derivative provides acyclic precursors that after deprotection undergoes a 6-endo-trig cyclization to yield the desired 2*H*-quinolizin-2-one derivative. This synthetic strategy was found to be generally applicable as evidenced from the various examples in this letter.

The 2*H*-quinolizin-2-one scaffold[1] can be an attractive structural template for drug discovery. Calculated low Log *D*[2] (0.8 at all pH) values for this charge neutral molecule were as surprising as they were encouraging. The origin of low Log *D* values lies in the very large dipole moment,[3] characteristic of the quinolizin-2-one scaffold which in turn arises aromaticity driven net internal charge separation. Compared to closely related drug discovery platforms such as corresponding hydroxy naphthalene, hydroxy quinoline or pyrimido-pyridine derivatives (Fig. 1), the 2*H*-quinolizin-2-ones were found to be significantly more polar as judged by HPLC and TLC retention times and greater solubilities.

Despite the appeal offered by the 2*H*-quinolizin-2-one scaffold, its use as a template for drug discovery has largely been unexplored. The paucity of synthetic methodology to access these structures readily is thought to be the main obstacle. In connection with a recent medicinal chemistry program, a 2*H*-quinolizin-2-one structural motif was designed as part of a drug discovery platform. The unique properties that manifested in the resulting drug molecules attributable to 2*H*-quinolizinones created increased interest. In order to exploit this finding, we were faced with the task of accessing quinolizin-2-ones in a straightforward and general fashion. A search of the literature revealed two synthetic strategies. Fozard and Jones[4] were able to displace bromo-quinolizinium salts with silver acetate followed by hydrolysis of the corresponding acetoxy group to unravel the desired quinolizin-2-one. Not only was the bromine displacement a low yielding reaction, but also this strategy demands the synthesis of corresponding bromo-quinolizinium salt, which poses enormous limitations

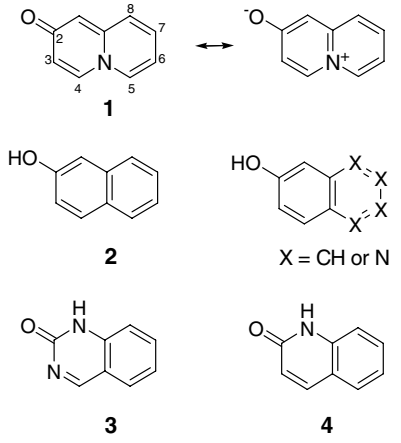
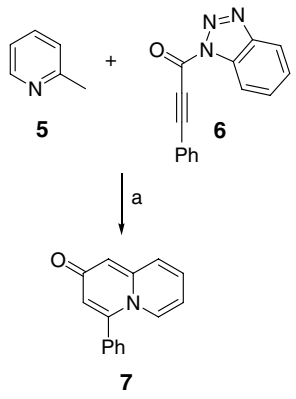


Figure 1. 2*H*-quinolizin-2-one canonical structures and representative structures of closely related platforms.

* Corresponding authors. Tel.: +1 732 594 0939; fax: +1 732 594 8080; e-mail: ravi_natarajan@merck.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.089



Scheme 1. Katritzky approach to the 2*H*-quinolizin-2-one scaffold. Reagents and conditions: (a) MeCN, sealed tube, 120 °C, 12 h.

on the utility of this synthetic approach. Kato and Atsumi[5] achieved the synthesis of the quinolizin-2-one scaffold by means of condensation of pyridylacetonitrile derivatives with diketene. This approach is conceptually simple but offers limited operational flexibility and generality.

In a more recent publication, Katritzky and co-workers[6] have reported a one pot synthetic approach (Scheme 1) to 2*H*-quinolizin-2-one core. Treatment of 2-picoline derivatives with a prepared 1,3-bis electrophile such as 1-benzotriazol-1-yl-3-propynone in a sealed tube at 120 °C for 12 h afforded modest yields of desired quinolizin-2-ones. Although this approach is relatively straightforward, sealed tube treatment at high temperatures may not be tolerant of a wide range of picoline and propynone derivatives. Furthermore, it requires a separate synthesis of specially activated benzotriazolyl propynoate, suggesting that readily available alkyl propynoates or the corresponding acid chlorides do not participate in this reaction thus restricting general applicability. In this communication a simple step-wise approach toward the assembly of 2*H*-quinolizin-2-one scaffold using commercially available 1,3-bis electrophiles is described.

Thus, base mediated deprotonation of 2-picoline (**5**) at low temperatures, followed by regioselective C-acylation of the resulting anion with a suitable 1,3-bis electrophile, was expected to give seco derivative (Fig. 2) which is set up to undergo a 6-endo-cyclization to furnish the desired quinolizin-2-one scaffold in the same reaction. In the event the ring closure did not occur spontaneously as anticipated, it could be induced thermally in a separate step. The depicted strategy is expected to be virtually tolerant of most 2-picoline derivatives and will represent a general approach to access all types of quinolizin-2-ones. The scope of this approach will be dictated by the choice of 1,3-bis electrophilic synthon selected for the synthesis and the ease of operation.

Initial C-acylation reactions were attempted with readily available 3-chloro-propionyl chloride, 3-ethoxy-methyl acrylate, and 3-trimethylsilyl methyl propynoate as the 1,3-bis electrophilic synthons. The former was expected

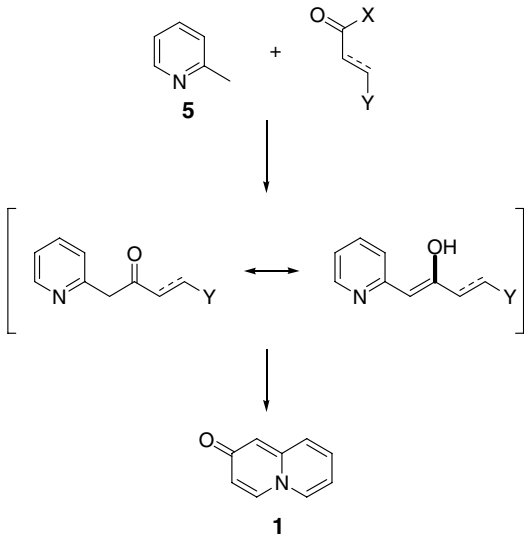
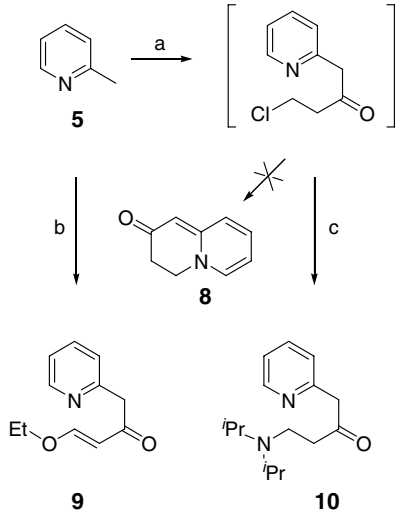
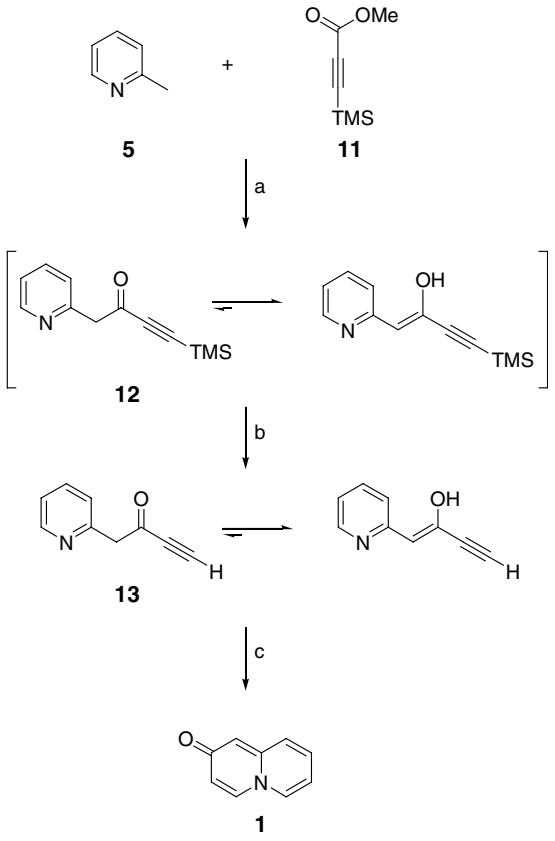


Figure 2. Strategy toward the 2*H*-quinolizin-2-one scaffold.

to furnish dihydro-quinolizin-2-one derivatives (Scheme 2). Thus, treatment of 2-picolinyl anion, generated by deprotonation with 2.1 equiv of LDA at −78 °C, with 1.1 equiv of 3-chloro-propionyl chloride, gave the expected C-acylation derivative but the product isolated after a standard work-up was the diisopropyl amine adduct **10** and not the desired cyclized di-hydro quinolizin-2-one (**8**). Competing displacement of pendant chloride by diisopropyl amine can be solved by the use of LiHMDS as the base in this reaction instead. This was not explored at the time of this publication. When 3-ethoxy-methyl acrylate was used as the electrophile, the C-acylated seco product was isolated in a clean reaction. The cylization was induced cleanly in a separate step by heating at 120 °C in methanol.



Scheme 2. Acylation of 2-picoline. Reagents and conditions: (a) 2.1 equiv of LDA, −78 °C, THF, 0.5 h then 1.1 equiv of 3-chloro-propionyl chloride, −78 °C to rt, 1 h, 45%. (b) 2.1 equiv of LDA, −78 °C, THF, 0.5 h then 1.1 equiv of 3-methoxy-methyl acrylate, −78 °C to rt, 1 h, 53%.



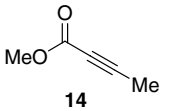
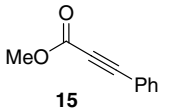
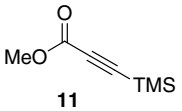
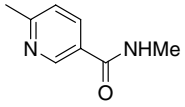
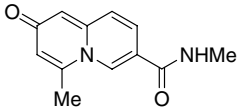
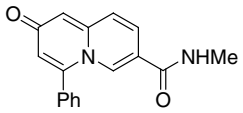
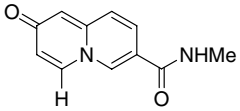
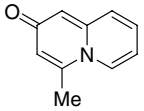
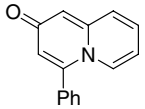
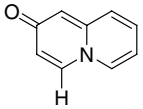
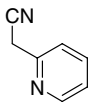
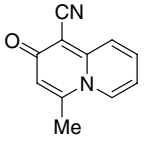
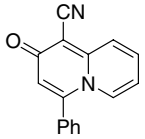
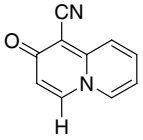
Scheme 3. Assembly of the 2*H*-quinolizin-2-one scaffold. Reagents and conditions: (a) 2.1 equiv of LDA, −78 °C, THF, 0.5 h then 1.1 equiv of 3-TMS-CCCOOMe, −78 °C to rt, 1 h, 85%. (b) 1.1 equiv of TBAF, THF, rt, 0.5 h, 80%. (c) 50 °C, MeCN, 100%.

In the use of 3-trimethylsilyl propynoate as the 1,3-bis electrophile it was noted that the product of initial C-acylation might not cyclize owing to geometric and steric considerations and that the ring closure might have to be effected in a separate step under forcing conditions. Thus treatment of 2-picolinyl anion with 1.5 equiv of β-TMS methyl propynoate at −78 °C gave after standard aqueous work-up the C-acylated product **12** exclusively in 85% yield. The absence of the picolinyl methylene proton in the ^{1}H NMR spectrum (CD_3OD) is conspicuous as the molecule exists predominantly in its enolized form. The chemical shift of the methyne proton of the enolized tautomer was at 5.72 ppm. Attempts to carry out the cyclization of **12** were largely unsuccessful as anticipated. Upon removal of the silyl protecting group the cyclization precursor **13** was obtained which underwent a surprisingly facile ring closure upon heating to 50 °C for 0.5 h (Scheme 3). The overall yield for annulation of a 1,3-bis electrophile such as 3-TMS-propynoate onto 2-picoline was 60%.

Further discussions will involve this reaction utilizing propynoates as electrophiles. The use of methoxy acrylates and 3-chloropropionyl chlorides as electrophiles are still under investigation and will be reported separately.

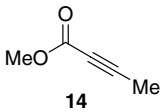
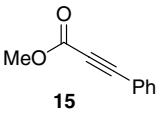
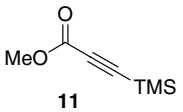
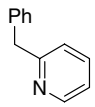
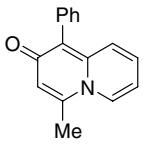
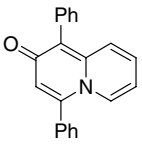
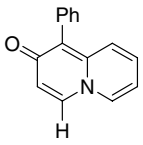
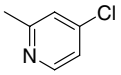
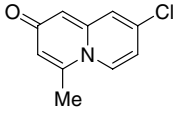
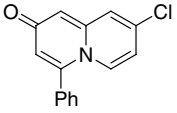
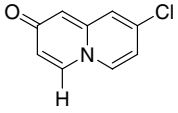
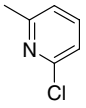
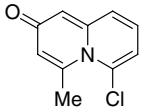
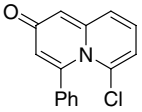
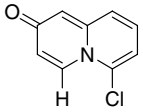
Apart from 3-trimethyl silyl propynoate, the use of 3-methyl propynoate (**14**) and 3-phenyl propynoate (**15**) were also investigated in these annulation reactions. As can be seen in Table 1 (Ref.[7]) a representative set of six 2-picoline derivatives were used as test substrates. These picoline substrates can be divided into two

Table 1. Selected examples of quinolizin-2-ones using the indicated picoline starting materials and propynoate electrophiles

	 **14**	 **15**	 **11**
 **16**	 **21** (45)	 **22** (35)	 **23** (48)
 **5**	 **24** (52)	 **7** (39)	 **1** (60)
 **17**	 **25** (49)	 **26** (37)	 **27** (50)

(*continued on next page*)

Table 1 (*continued*)

	 **14**	 **15**	 **11**
 **18**	 **28** (55)	 **29** (33)	 **30** (46)
 **19**	 **31** (53)	 **32** (23)	 **33** (45)
 **20**	 **34** (41)	 **35** (36)	 **36** (43)

Numbers in parentheses are uncorrected overall yields.

groups. Compounds **16**, **5**, **17**, and **18** bear a nucleophilic pyridine moiety while in **19** and **20** the chlorine substituents at the 2- and 4- positions attenuate the nucleophilicity of the pyridine nitrogen atom. In reactions with 3-methyl propynoate **14**, after the initial acylation ring closure was found to occur spontaneously. In some examples, the crude reaction had to be heated to 100 °C to complete the ring closure reaction. In the reaction with **15** it was necessary to heat the reactions to effect ring closure. The use of propynoate **11** gave seco products that could be isolated cleanly. Removal of TMS protecting group was carried out first in order to effect ring closure in these examples. Weinreb amide derivatives could also be used as effective acylating agents.

In addition to the examples shown in Table 1, this reaction sequence was extended to encompass the synthesis of aza-analogs of the quinolizin-2-one template. As indicated in Figure 3 3-methyl pyridazine, 4-methyl pyrimidine, and 3-methyl pyrazines underwent smooth deprotonation under the usual conditions and were successfully acylated with 3-methyl propynoate to yield the corresponding aza-quinolizin-2-one, respectively, in modest to good overall yields as indicated.

In conclusion, a straightforward strategy toward the assembly of quinolizin-2-one template has been devised. This method is expected to allow easy access to virtually all kinds of quinolizin-2-ones by appropriate choice of starting picoline derivative and 1,3-bis electrophile. The mild reaction conditions used is expected to be tolerant of all kinds of functional groups except carboxylic acid esters. This methodology has also been extended to aza-

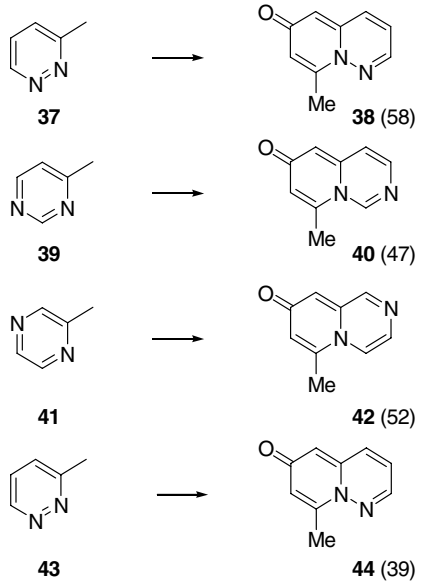


Figure 3. Aza-analogs of the quinolizin-2-one scaffold.

analogs with ease. Considering the value brought to any drug discovery program by designing these substructures into drug molecules, it is expected that this strategy will get the opportunity for further improvements.

References and notes

1. For use of benzo-quinolizinones as CFTR channel inhibitors see Marivingt-Mounir, C.; Norez, C.; Derand, R.;

Bulteau-Pignoux, L.; Nguyen-Huy, D.; Viossat, B.; Morgant, G.; Becq, F.; Vierfond, J.-M.; Mettey, Y. *J. Med. Chem.* **2004**, *47*, 962, and references therein.
2. Calculated values determined using ACD Labs. The calculated Log*D* values for hydroxy naphthalene, hydroxy quinoline, and pyrimido-pyrimidine templates as indicated in Figure 1 range from 1.5 to 2.5 at pH 7. Experimentally determined Log*D* values for similar analogs are in agreement.
3. Calculated dipole moments for the 2*H*-quinolizinone scaffold (**1**) was 7.5 Debye units compared to hydroxy naphthalene (**2**), hydroxy quinoline (**3**), and pyrimido-pyrimidine (**4**) at 1.7, 6.7, and 4.6 Debye units, respectively.
4. (a) Fozard, A.; Jones, G. *J. Chem. Soc. Abstr.* **1964**, 2760–2763; (b) Sanders, G. M.; Van Dijk, M.; Vander Plas, H. C. *Heterocycles* **1981**, *15*, 213; (c) Ihmels, H. *Sci. Synth.* **2005**, *15*, 907.
5. Kato, T.; Atsumi, T. *Chem. Abstr.* **1968**, *68*, 49422g.
6. (a) Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair, S. K. *ARKIVOC* **2004**, *viii*, 52–60; (b) Murthi, G. S. S.; Gangopadhyay, S. K. *Indian J. Chem.* **1979**, *17*, 20.
7. Representative procedure: synthesis of **7**. 2-Picoline (1 mmol) was dissolved in 15 mL of dry THF, cooled to −78 °C, and deprotonated with 2.1 mmol of freshly made LDA. After 0.5 h the reaction was quenched with 1.5 mmol of propynoate **15**. The reaction was allowed to warm-up to rt over 4 h and quenched by addition of satd ammonium chloride. Standard aqueous work-up followed by heating the crude in acetonitrile at 80 °C furnished the product. After removal of solvent the residue was purified by silica gel chromatography using 1–5% methanol in acetone to give desired product **7** in 39% yield. ^{1}H NMR (CD_3OD): 8.58 (d, $J = 9.6$ Hz, 1H); 8.20 (m, 1H); 8.01 (m, 1H); 7.71–7.52 (m, 6H); 7.49 (m, 2H).