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Quinoline synthesis by improved Skraup–Doebner–Von Miller reactions utilizing acrolein diethyl acetal

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ABSTRACT

A robust synthetic method has been developed as an improvement to the venerable Skraup–Doebner–Von Miller reaction providing access to various quinoline products. The straightforward procedure utilizes acrolein diethyl acetal as a three-carbon annulation partner with aniline substrates in a monophasic, organic solvent-free reaction medium. Differentially substituted aniline precursors were found to be compatible with the reaction conditions and the corresponding quinoline products are isolated in moderate to good yields.

Introduction

Substituted quinolines are ubiquitous motifs in various classes of biologically active organic compounds. Historically, successful medicinal application of quinoline-containing natural and synthetic materials has focused on treatments for malaria.[1] However, broader application of these molecules has also been achieved. In fact, a recent study found the quinoline moiety as a top 5 most prevalent six-membered nitrogen heterocycle present in a database of 1994 FDA approved pharmaceutials.[2] In addition to possessing interesting biological activities, appropriately substituted quinoline rings have found application as antioxidants,[3] synthetic dyes,[4] and chiral small molecule catalysts.[5] Thus, the development of efficient synthetic methods for the preparation of this fused heterocyclic ring system is a focus of many research efforts.

Recent progress in this field has included improvements to classical reactions used to prepare quinoline-containing systems and include contributions to the Combes,[6] Conrad–Limpach,[7] and Skraup[8] reactions in addition to the Doebner–Von Miller,[9] Friedlander,[10] and Pfitzinger[11] quinoline syntheses.[12] As part of a research program focused on the synthesis of diverse quinolines, we became interested in the mechanistically related Skraup and Doebner–Von Miller (DVM) protocols. Both methods utilize aniline starting materials and either glycerol (Skraup) or α,β-unsaturated aldehyde (DVM) annulation partners. As depicted in Scheme 1, acidic and thermal conditions are typically employed for each reaction. The DVM process is arguably more synthetically attractive because strong exogenous oxidants are not typically required and reaction workup procedures are straightforward. Additionally, the reaction tolerates β-substitution on the enal reaction partner leading to diverse quinoline products substituted at C2 if desired (R_2 in Scheme 1).

However, if quinoline products unsubstituted at C2, C3, and C4 are desired, acrolein must be used as the three-carbon enal reaction partner. Drawbacks of this method include acrolein's relatively high cost[13] and propensity to oligomerize under the DVM reaction conditions (even after prolonged storage at 4 °C). This necessitates the use of excess reagent and results in tedious workup and purification steps to obtain the quinoline products. In this work, we have established a straightforward and general DVM synthesis of various quinoline products using the diethyl acetal of acrolein as an annulation partner.[14] The reactions tolerate substitution of the aniline ring and proceed in generally higher yields than typical DVM reactions with enal reaction partners.

We began our studies of the DVM reaction of aniline (**1**) and acrolein (**2**; 2 equiv) in a biphasic mixture of equal volumes of toluene and 6N hydrochloric acid (HCl) at elevated temperature. This biphasic solvent system has been shown as advantageous for DVM reaction efficiency.[9] As seen in Table 1, these conditions provided <10% of isolated quinoline product **3** after ca. 1 day reaction time at 111 °C at either 0.50 or 0.25 M concentration (entries 1 and 2). Substituting hydrochloric acid with either a Lewis acid or ammonium salt only provided trace amount of product in comparable time frames (entries 3 and 4). Diluting the reaction mixture and lowering the ratio of organic cosolvent gave improved results. For example, a 3.4:1 mixture of 6N HCl/toluene under otherwise similar conditions provided a 28% yield of quinoline (entry 5).

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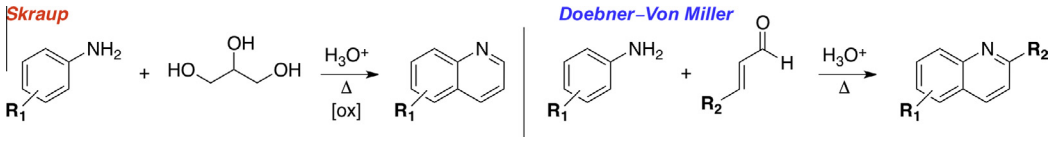
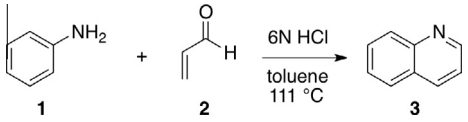


Scheme 1. Skraup and Doebner–Von Miller reactions.

Table 1
Initial optimization studies



1 2 3

Entry	6N HCl/toluene	Concentration[a] (M)	Yield[b] (%)
1	1:1	0.50	2
2	1:1	0.25	9
3[c]	—	0.20	Trace
4[d]	—	0.25	Trace
5	3.4:1	0.06	28
6	6.9:1	0.06	35
7	6N HCl only	0.06	Trace

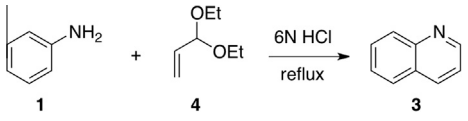
[a] Aniline concentration.
[b] Isolated yields.
[c] Reaction run with 3 equiv $AlCl_3$ in CH_2Cl_2 for 24 h at 23 °C.
[d] Reaction run with 10 mol % NH_4Cl in toluene for 24 h at 50 °C.

Decreasing the ratio of organic solvent to a 6.9:1 mixture of 6N HCl/toluene improved the isolated yield of quinoline to 35% (entry 6). Unfortunately, removing the organic solvent entirely was detrimental to the reaction outcome (entry 7).

At this point, no further increase in product yield was achieved by modifying variables such as time, concentration, or temperature. However, a significant increase in reaction efficiency was discovered upon substitution of acrolein with acrolein diethyl acetal. Running the reaction under otherwise optimal biphasic conditions led to an isolated quinoline yield of 25% (entry 1, Table 2). This was comparable to the reaction with acrolein (cf. entry 5, Table 1). However, unlike the DVM reaction using acrolein, a significant increase in product yield was now observed upon omission of the organic cosolvent. Specifically, the product quinoline was isolated in 54% yield after a reaction time of 24 h in 6N HCl (entry 2, Table 2). Diluting the reaction mixture to 0.01 M and using less concentrated 1N HCl resulted in a similar yield but greatly facilitated isolation of product (entry 3). Shorter reaction times decreased product yields (entries 4 and 5) while a longer reaction time did not significantly increase yield (entry 6).

Having identified acrolein diethyl acetal as a robust substitute for acrolein, the substrate scope with respect to starting aniline was investigated. The toluidine series provided alkylated quinoline products in modest to good yields (Table 3, entries 1–3). For example, DVM reaction between *o*-toluidine (**5**) and acrolein diethyl acetal was quite efficient, providing the substituted quinoline product **6** in 83% yield (entry 1). On the other hand, *p*-toluidine (**7**) reacted with **4** to provide a lower 36% yield of quinoline product **8** (entry 2). Interestingly, when *m*-toluidine (**9**) was subjected to the optimized reaction conditions a ca. 1:1 mixture of 5-methylquinoline (**10a**) and 7-methylquinoline (**10b**) was isolated in a combined 16% yield (entry 3). Halogenated anilines also participated in the DVM reaction with similar efficiencies. Utilizing 2-bromoaniline (**11**) in the DVM reaction with **4** provided 21% yield

Table 2
DVM reaction with acrolein diethyl acetal

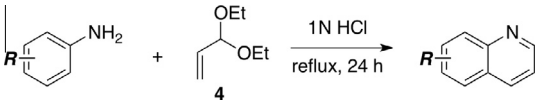


1 4 3

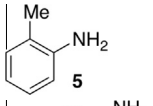
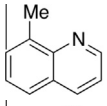
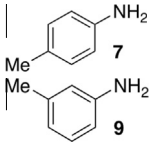
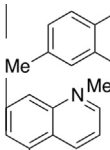
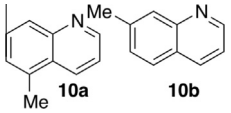
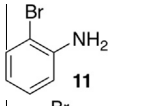
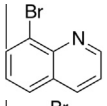
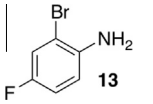
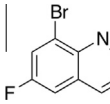
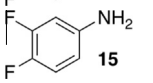
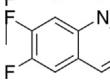
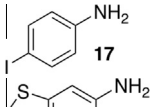
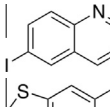
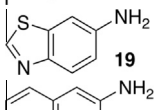
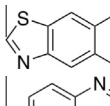
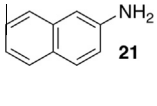
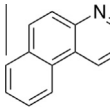
Entry	Concentration[a] (M)	Time (h)	Yield[b] (%)
1[c]	0.06	24	25
2	0.07	24	54
3	0.01	24	56
4	0.07	6	25
5	0.07	3	21
6	0.07	67	63

[a] Aniline concentration.
[b] Isolated yields.
[c] Reaction run using a 3.4:1 mixture of 6N HCl/toluene.

Table 3
Aniline substrate scope with acrolein diethyl acetal

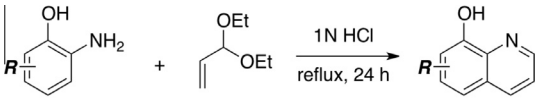


4

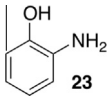
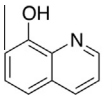
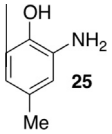
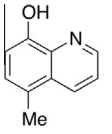
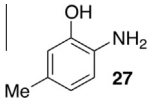
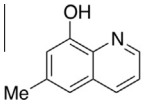
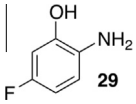
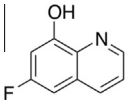
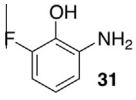
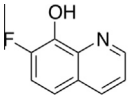
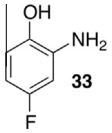
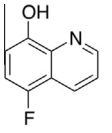
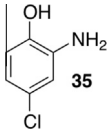
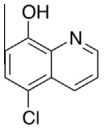
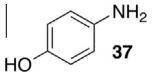
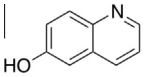
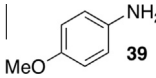
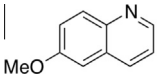
Entry	Aniline	Product	Yield[a] (%)
1	 5	 6	83
2	 7	 8	36
3	9	 10a 10b	16[b]
4	 11	 12	21
5	 13	 14	55
6	 15	 16	16
7	 17	 18	10
8	 19	 20	21
9	 21	 22	46

[a] Isolated yields after silica gel chromatography.
[b] Isolated as a ca. 1:1 ratio of **10a**:**10b**.

Table 4
Aminophenol Subtract Scope with **4**



4

Entry	Aniline	Product	Yield[a] (%)
1	 **23**	 **24**	41
2	 **25**	 **26**	58
3	 **27**	 **28**	50
4	 **29**	 **30**	42
5	 **31**	 **32**	43
6	 **33**	 **34**	18
7	 **35**	 **36**	49
8	 **37**	 **38**	23
9	 **39**	 **40**	27

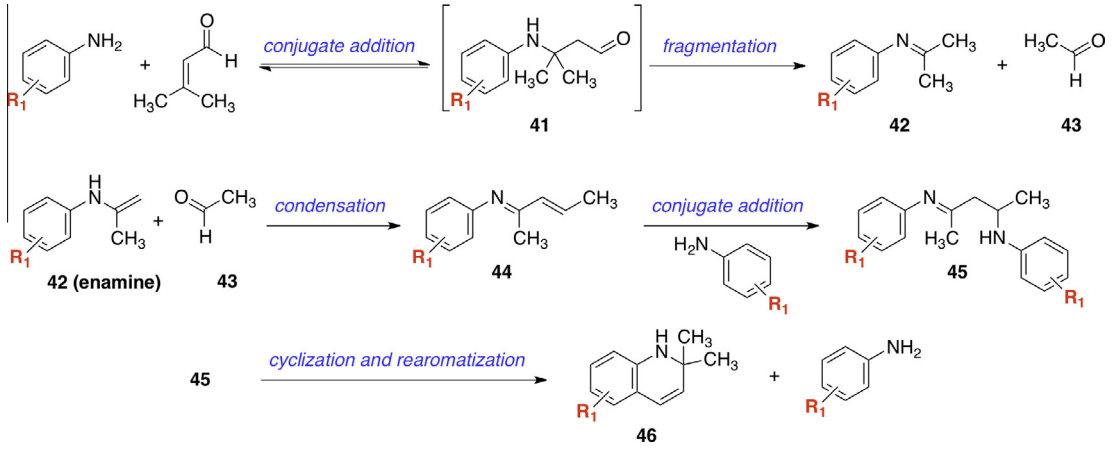
[a] Isolated yields after silica gel chromatography.

of quinoline product **12** (entry 4). Starting with 2-bromo-4-fluoroaniline (**13**), quinoline product **14** was isolated in 55% yield following the DVM reaction (entry 5). The difluorinated aniline **15** as well as 4-iodoanline (**17**) substrates were less efficient, delivering products **16** and **18** in modest 16% and 10% yields, respectively (entries 6 and 7). A heterocyclic aniline containing a thiazole ring (**19**) has been studied in the DVM reaction with **4** providing tricyclic product **20** in 21% yield (entry 8). An additional tricyclic product was formed from reaction of 2-naphthylaniline (**21**) with **4** providing product **22** in 46% yield (entry 9).

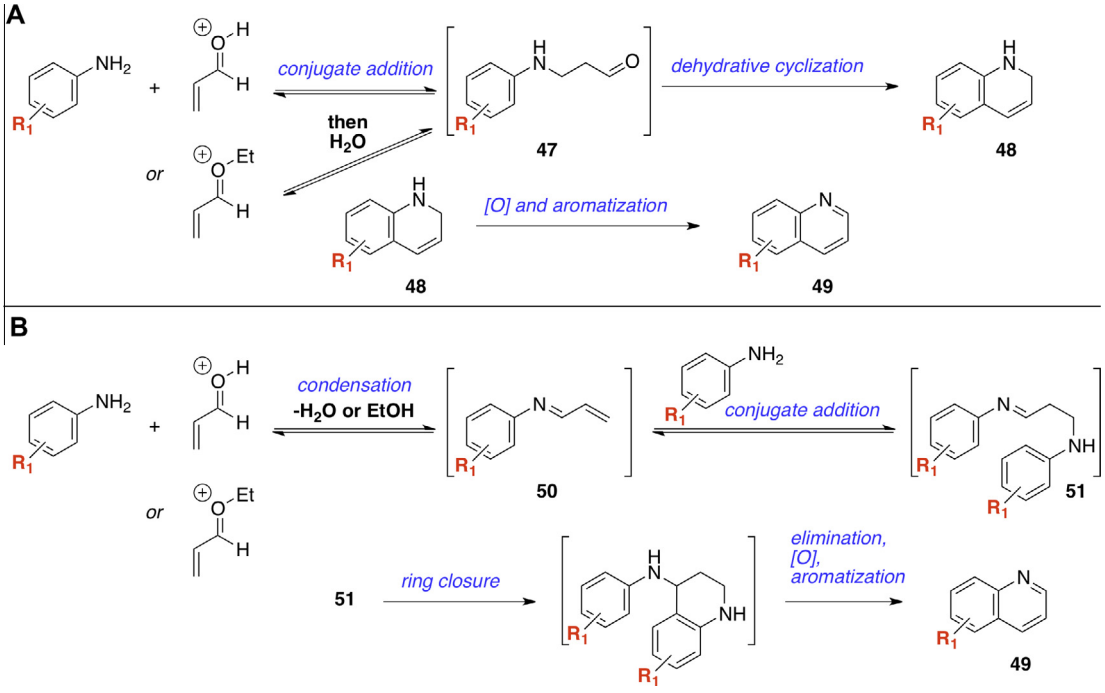
Diversification of the substrate scope was next investigated by incorporating phenolic groups into the starting materials (Table 4). The hydroxyquinoline products obtained from such DVM reactions are known to be metal chelators with a variety of applications.[15] As such, 2-aminophenol (**23**) smoothly underwent the annulation reaction to deliver 8-hydroxyquinoline (**24**) in 41% isolated yield (entry 1). Better results were obtained with 2-amino-4-methylphenol (**25**) and 2-amino-5-methylphenol (**27**) delivering products **26** and **28** in 58% and 50% yields, respectively (entries 2 and 3). Fluorinated derivatives were good reaction partners as well with 5-fluoro-2-aminophenol (**29**) delivering the corresponding quinoline product **30** in 42% yield (entry 4). The regioisomer 6-fluoro-2-aminophenol (**31**) was as efficient (43% yield of product **32**, entry 5), with the 4-fluoro-2-aminophenol (**33**) isomer less so (18% yield of product **34**, entry 6). Chlorination was also tolerated with 4-chloro-2-aminophenol (**35**) reacting with **4** to provide quinoline **36** in 49% yield (entry 7). Alternatively, starting with 4-aminophenol (**37**) reduced overall efficiency leading to product **38** in 23% yield (entry 8). The 4-methoxyphenol derivative **39** performed similarly in the DVM process to give quinoline **40** in 27% yield (entry 9).

The mechanistic details of the Skraup and DVM reactions have been the subject of much investigation and debate in the literature.[16] Most recently, Denmark and coworkers proposed that a conjugate addition–fragmentation mechanism was operative when β-disubstituted carbonyl substrates were employed in the reaction.[17] This proposal was supported with careful crossover experiments using ^{13}C-labeled substrates. While Denmark studied ketone derivatives, if applied to β-disubstituted enals their mechanism would begin with reversible conjugate addition with the aniline to deliver intermediate **41** (Scheme 2). Next, irreversible fragmentation to imine **42** and acetaldehyde (**43**) would be followed with recombination through the enamine tautomer of **42**. The product of this recombination, **44**, would be subject to conjugate addition of aniline to give **45** which would then cyclize to deliver the dehydroquinoline product **46** and aniline.

Since the current system employs acrolein derivatives unsubstituted at the β-position, the fragmentation as proposed by Denmark would be unproductive because the analogous enamine required



Scheme 2. Proposed mechanism for the DVM reaction with β-disubstituted carbonyl compound.



Scheme 3. Proposed mechanism for the DVM reaction acrolein diethyl acetal.

for recombination is inaccessible. Hence, conjugate addition to the protonated acrolein (or oxocarbenium ion[18]) would deliver **47** that would be followed by direct dehydrative ring closure to give **48** (Scheme 3A). Oxidative aromatization would then provide the product quinoline **49**. Alternatively, we cannot rule out the formation of anil **50** first through a condensation reaction which then can undergo conjugate addition from aniline to give **51** (Scheme 3B). Ring closure, aniline elimination, and oxidative aromatization would then deliver the product.

In conclusion, we have identified an operationally simple method for efficient DVM annulations using the diethyl acetal of acrolein. Products are isolated in modest to good yields, and the reaction tolerates a range of different functional groups including alkyl groups, halogens, phenols, and heterocycles. New fluorinated quinolines may have applications in medicinal chemistry, while novel hydroxyquinoline products prepared herein are predicted to have interesting metal binding activity.

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Supplementary data

General experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for quinoline products **14**, **16**, **18**, **20**, **26**, **28**, **30**, **32**, and **34** are available online. Additionally, copies of ^{1}H NMR spectra for known quinoline products **3**, **6**, **8**, **10a** + **10b**, **12**, **22**, **24**, **36**, and **38** are also available online.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.145.

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14. A 96% pure sample of acrolein diethyl acetal from Sigma–Aldrich costs $66.40/25 g and does not require a stabilizer for prolonged storage. (Prices accessed July, 2015).
15. For an example, see: Farruggia, G.; Iotti, S.; Prodi, L.; Montalti, M.; Zaccheroni, N.; Savage, P. B.; Trapani, V.; Sale, P.; Wolf, F. I. *J. Am. Chem. Soc.* **2006**, *128*, 344–350.
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