Tetrahedron Letters 49 (2008) 6893–6895

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Base-mediated synthesis of quinolines: an unexpected cyclization reaction between 2-aminobenzylalcohol and ketones

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ARTICLE INFO

Article history:
Received 11 August 2008
Revised 15 September 2008
Accepted 17 September 2008
Available online 20 September 2008

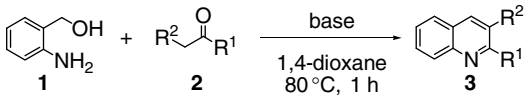
Keywords:
Quinolines
Hydrogen transfer
Friedlander
Oppenauer oxidation

ABSTRACT

Quinolines are prepared in an oxidative cyclization reaction between 2-aminobenzylalcohol and ketones. This reaction, that involves a hydrogen transfer, is mediated solely by a base without the need for a transition metal catalyst.

Many compounds containing the quinoline scaffold exhibit a wide variety of pharmacological and biological activities. Members of this family are currently used in medicinal chemistry as antimalarial,[1] anti-inflammatory,[2] antiasthmatic,[3] anti-bacterial,[4] antihypertensive,[5] anticancer,[6] and tyrosine kinase inhibitory agents.[7] In addition, quinoline-based polymers find applications in the fields of electronics, optoelectronics, and nonlinear optics.[8] Consequently, efforts for their synthesis are still increasing. Over the last few decades, research has shifted from the conventional named methods such as the Skraup, Doebner-von Miller, Conrad-Limpach, Pfitzinger, and Friedländer syntheses to more efficient organometal-catalyzed approaches.[9] In a modification of the Friedländer method, 2-aminobenzylalcohol (**1**) is oxidatively cyclized with ketones yielding substituted quinolines in the presence of a ruthenium catalyst and a base.[9e] The addition of benzophenone was found to enhance this process.[9f,g] In our previous reports,[10] we had shown that $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$, also known as the second generation Grubbs catalyst, in combination with KO*t*Bu gives the best results thus far in terms of yield and reaction time.

In this Letter, we present for the first time that this reaction also proceeds in the absence of a transition metal catalyst and that it can be mediated solely by a strong base. This is highly remarkable, since this method involves a hydrogen transfer reaction for the in situ oxidation of **1** to 2-aminobenzaldehyde which is normally catalyzed by a transition metal. Thus, we now report the base-mediated cyclization reaction between **1** and ketones to afford quinolines in the absence of an expensive transition metal catalyst (Scheme 1).



Scheme 1. General reaction scheme.

The performance of several bases was examined for the reaction between **1** and acetophenone (**2a**, R^1 = Ph, R^2 = H). The results are shown in Figure 1. The highest quinoline yields are obtained with the stronger bases KO*t*Bu, NaH, and NaOEt. The reaction does not proceed in the absence of a base.

A variety of ketones were coupled with **1** in the presence of the bases KO*t*Bu, NaOEt, or NaH. The results after 1 h of reaction are presented in Table 1. It is clear that the highest quinoline yields are obtained with KO*t*Bu. Although Figure 1 suggests that NaH gives higher yields after 4 h, the use of NaH is somewhat hindered by the evolution of hydrogen gas, making the solution foam.

The presence of a substituent on the aromatic ring of acetophenone results in lower yields (entries 2–6), whereas the 2′, 3′, and 4′ methyl-substituted compounds have comparable yields, the difference between 2′ and 4′ methoxy-substituted acetophenone is remarkable. With an *ortho*-substituted ketone the yield is twice as high compared to a *para*-substituted ketone.

When two different α-protons are available in a ketone, a mixture of two quinolines is obtained (see entries 8 and 9). While the use of KO*t*Bu gives higher yields, the selectivity is lower. For 2-heptanone, the ratios are 1.8:1 for KO*t*Bu versus 3.3:1 and 4.2:1 for

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doi:10.1016/j.tetlet.2008.09.103

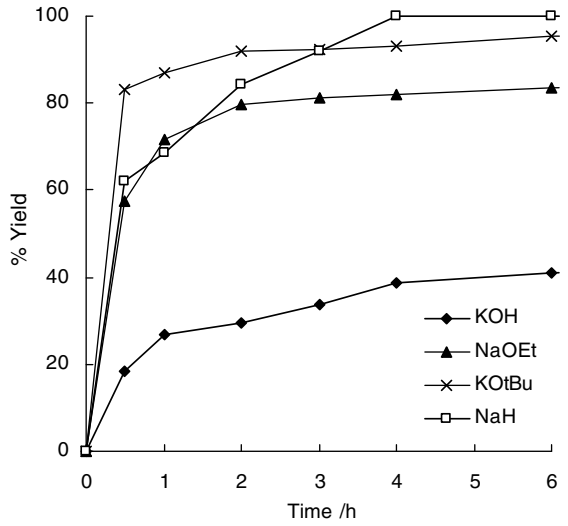
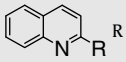
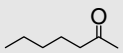
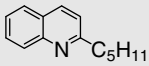
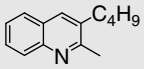
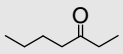
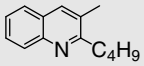
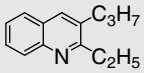
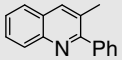
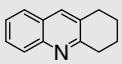


Figure 1. Base-mediated quinoline synthesis. Reaction conditions: **1** (1.0 mmol), **2a** (2.0 mmol) and base (1.5 mmol) in 3 ml 1,4-dioxane at 80 °C. Yields determined by GC with dodecane as internal standard.

Table 1
Base-mediated quinoline synthesis from 2-aminobenzylalcohol and a variety of ketones[a]

Entry	Ketone	Quinoline	Yield[b] (%)		
			KO*t*Bu	NaOEt	NaH
1	 R = Ph (**2a**)	 R = Ph	94	63	64
2	2-MeC_6H_4	2-MeC_6H_4	65	40	58
3	3-MeC_6H_4	3-MeC_6H_4	59	50	53
4	4-MeC_6H_4	4-MeC_6H_4	62	42	34
5	2-MeOC_6H_4	2-MeOC_6H_4	99	53	60
6	4-MeOC_6H_4	4-MeOC_6H_4	47	27	38
7	Me[c]	Me	17	19	22
8			30	23	25
			17	7	6
9			61	19	43
			15	3	7
10			83	39	49
11			51	29	39

[a] Reaction conditions: **1** (1.0 mmol), ketone (2.0 mmol) and base (1.5 mmol) in 3 ml 1,4-dioxane at 80 °C for 1 h.
[b] Yields based on **1** determined by GC with dodecane as internal standard.
[c] 5 mmol.

NaOEt and NaH, respectively. A similar effect is observed for 3-heptanone.

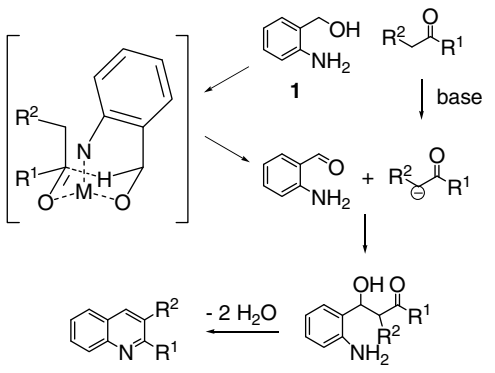
In comparison to the ruthenium-catalyzed reactions,[10] the yields obtained with acetone (entry 7) and 2-heptanone (entry 8) are markedly lower. This is the result of self-condensation of the ketones in a base-catalyzed aldol condensation whereby α,β-unsaturated ketones are formed.[11] This self-condensation is much less pronounced with the other ketones, and it is not observed in the ruthenium-catalyzed process. Thus, the formation of quinoline is in competition with the aforementioned aldol reaction. When 2-heptanone is gradually added to a reaction mixture containing **1** and KO*t*Bu in dioxane, the aldol reaction is suppressed and quinoline yields of 56% and 28% are obtained for 2-pentylquinoline and 3-butyl-2-methyl-quinoline, respectively.

After 2 h of reaction, the yields of all quinolines slightly increase with 5–10% and they continue to increase over time. This can be rationalized as follows. Once the initial stronger base is consumed, the reaction continues at a slower rate with OH^-. This hydroxy anion is most likely produced in the reaction between the strong base and a H_2O molecule that is liberated in the final cyclization step of the global reaction (see Scheme 2). This suggests that this reaction is in fact base-catalyzed. Further support for this base-catalyzed mechanism is found, when **1** (1.0 mmol) is reacted with **2a** (2.0 mmol) with only 0.50 mmol KO*t*Bu. After 1 h, the yield is 45%, but after 6 h the yield has increased to 59% which can only mean a base is still present in the reaction mixture.

Although the exact mechanism of this reaction is not yet fully understood, it certainly involves a hydrogen transfer, as the GC chromatograms clearly show conversion of the ketones into the corresponding alcohols during the reaction. It is believed that a mechanism similar to that of Meerwein–Ponndorf–Verley (MPV) reduction or Oppenauer oxidation may be responsible for this. Purely base-catalyzed MPV reductions with KO*t*Bu and H_2 have been reported under very demanding reaction conditions with temperatures of 150–200 °C, high H_2 pressures, and reaction times of several hours.[12] Uncatalyzed hydrogen transfer reactions at high temperatures mediated by alcohols also exist.[13] To our knowledge, this is the first report of a relatively mild base-mediated transfer hydrogenation reaction between an alcohol and a ketone, in the absence of a transition metal catalyst, that affords the quinoline nucleus.

The amine function of **1** seems to play an important role, since the reaction of benzylalcohol (**3**) with ketones did not produce any coupling products. For instance, the reaction between **3** and **2a** should produce chalcone or 3-phenylpropiophenone as was described in our previous report on the ruthenium-catalyzed process.[10a] Neither of these compounds was observed here, suggesting that the oxidation of **3** to benzaldehyde did not occur. This leads us to propose a reaction mechanism as shown in Scheme 2 (for clarity, unnecessary atoms have been omitted).

One equivalent of the ketone acts as hydrogen acceptor and is converted to the corresponding alcohol in the oxidation process of **1**. A cross aldol reaction between the aldehyde and deprotonated ketone, followed by a cyclization step, leads to the quinoline. The proposed intermediate is nearly identical to that of the MPV reduction, but an additional interaction between the amine and the alka-



Scheme 2. Proposed reaction mechanism and cyclic intermediate.

li cation might provide favorable conditions for the hydrogen transfer.

In a general procedure for quinoline synthesis, a mixture of ketone (2.0 mmol), 2-aminobenzylalcohol (1.0 mmol), dodecane (0.25 mmol), and the base (1.5 mmol) in 3 ml dioxane was placed in a 7 ml screw-capped vial and allowed to react at 80 °C for 1 h. To remove inorganic salts, the reaction mixture was filtered through a short silica gel column (ethyl acetate), and the yields were determined by GC analysis with dodecane as internal standard. When NaH was used, the vial was only placed at 80 °C after the initial evolution of hydrogen gas had ceased. The isolation and characterization of the prepared quinolines have been described previously.[10a]

In conclusion, we have shown for the first time that quinolines can be prepared by a base-mediated cyclization reaction between 2-aminobenzylalcohol and ketones in the absence of a transition metal catalyst. The highest yields are obtained with KO*t*Bu. A mechanism similar to that for the MPV reduction is suggested.

Acknowledgments

The authors gratefully acknowledge the Research Fund of Ghent University and the FWO Flanders (Fonds voor Watenschappelijk Onderzoek–Vlaanderen) for the financial support during the preparation of this Letter.

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