

Synthesis of quinaldines and lepidines by a Doebner–Miller reaction under thermal and microwave irradiation conditions using phosphotungstic acid

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Received 7 September 2005; revised 1 January 2006; accepted 11 January 2006

Available online 26 January 2006

Abstract—A simple and efficient method has been developed for the synthesis of quinaldines and lepidines by a one-pot reaction of anilines with crotonaldehyde or methyl vinyl ketone using phosphotungstic acid, a Keggin-type heteropoly acid, under both thermal and microwave irradiation conditions.

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As a large number of natural products¹ and drugs² contain a quinoline moiety, the synthesis of this heterocyclic nucleus and derivatives has been of considerable interest to organic and medicinal chemists for many years. Skrap-up's procedure³ which is the classical method for the synthesis of quinoline involves a large amount of sulfuric acid at temperatures above 150 °C and the reaction is often violent. Many other methods have been developed for the synthesis of quinolines but most are not fully satisfactory either with regard to yield or reaction conditions, generality or operational simplicity.⁴ The Doebner–Miller synthesis⁵ is frequently used in the preparation of a variety of quinoline derivatives³ due to its simplicity even though the yields are usually not high. The reaction also involves a tedious isolation procedure from the complex reaction mixture.⁶ The acid-catalyzed polymerization of the aldehyde lowers the yield and makes the isolation of the target product difficult. It was found that the Doebner–Miller reaction in a two-phase solvent system, an organic phase and an aqueous acid phase, decreases the polymerization of the aldehyde and brings a marked improvement in product isolation.⁷ Although the synthesis of quinolines using InCl₃ on a silica gel surface is simple and efficient under microwave irradiation conditions, conventional heating in place of microwave irradiation induces the

polymerization of vinyl ketones reducing the yield of quinolines drastically.⁸ Thus a simple, general and efficient procedure for the synthesis of this important heterocycle is still needed.

Heteropoly acids are economically and environmentally attractive. They have a very strong Bronsted acidity⁹ approaching the superacid region and exhibit a 'pseudo-liquid phase'.¹⁰ Keggin anions have a very weak basicity and great softness¹¹ and they stabilize cationic organic intermediates.¹² Heteropoly acids absorb a large amount of polar molecules like alcohols, ethers, amines, etc., forming heteropoly acid solvates.¹³ Heteropoly acids offer good options for more efficient and cleaner processing compared to conventional mineral acids.¹⁴ As stable, relatively non-toxic crystalline substances, heteropoly acids are also preferable with regard to safety and ease of handling. Heteropoly acids are promising solid acid catalyst for Friedel–Crafts reactions, Prins reaction,¹² Diels–Alder reaction,¹⁶ Beckman rearrangement under mild conditions,¹⁷ pinacol rearrangement,¹⁸ esterification,¹⁹ cyclotrimerisation of aldehydes²⁰ and for the synthesis of vitamins E, K1 and C.¹⁵ Prompted by these we have now examined the Doebner–Miller reaction using phosphotungstic acid.

This communication describes a simple and efficient method for the synthesis of quinaldines (**2a–n**) and lepidines (**2o–s**) by a one-pot reaction of anilines (**1a–s**) with α,β -unsaturated carbonyl compounds using phosphotungstic acid, a Keggin-type heteropoly acid, with

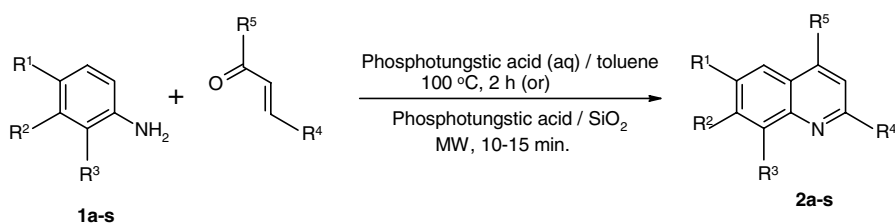
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Table 1. Quinoline derivatives produced by the Doebner–Miller reaction using phosphotungstic acid under thermal and microwave irradiation conditions

Entry	R ¹	R ²	R ³	R ⁴	R ⁵	Product	MWI time (min)	Yield ^a %	
								Δ ^b	MWI
1	H	H	H	CH ₃	H	2a	10	85	90
2	C ₂ H ₅	H	H	CH ₃	H	2b	10	80	84
3	OH	H	H	CH ₃	H	2c	10	85	89
4	H	H	OH	CH ₃	H	2d	12	81	85
5	NO ₂	H	H	CH ₃	H	2e	13	78	83
6	H	H	NO ₂	CH ₃	H	2f	15	75	79
7	Cl	H	H	CH ₃	H	2g	11	84	89
8	H	H	Cl	CH ₃	H	2h	13	81	86
9	Br	H	H	CH ₃	H	2i	12	86	90
10	OCH ₃	H	H	CH ₃	H	2j	10	89	94
11	H	H	OCH ₃	CH ₃	H	2k	12	84	90
12	H	Cl	H	CH ₃	H	2l	12	80	86
13	H	Br	H	CH ₃	H	2m	14	83	89
14	H	NO ₂	H	CH ₃	H	2n	13	82	88
15	H	Cl	H	H	CH ₃	2o	13	79	86
16	Cl	H	H	H	CH ₃	2p	14	74	80
17	H	H	Cl	H	CH ₃	2q	12	80	86
18	OCH ₃	H	H	H	CH ₃	2r	10	82	87
19	H	H	NO ₂	H	CH ₃	2s	11	81	87

^a All products were characterized by ¹H NMR, ¹³C NMR, IR and mass spectra.

^b The reaction mixture was stirred at 100 °C for 2 h with conventional heating.



conventional heating as well as microwave irradiation.²¹ The results are presented in Table 1.

In general, the yields of quinaldines and lepidines were little affected by the nature of substituents on the aniline. Presumably, the process involves Michael addition of the aniline to α,β -unsaturated carbonyl compound²² followed by subsequent cyclization and aromatization²³ under the catalysis of phosphotungstic acid.

The reaction also works with anilines in which an electron-withdrawing group is situated *ortho* or *para* to the point of electrophilic ring closure. In case of *m*-substituted chloro and bromo anilines the electrophilic ring closure occurs at the *para* position resulting in the formation of the 7-substituted product whereas in case of *m*-nitroanilines the electrophilic ring closure occurs *ortho* to the nitro group resulting in the formation of the 5-substituted product.²⁴ The reaction also works with enones like methyl vinyl ketone. However, this reaction does not proceed with highly polymerisable substrates like acrolein and propenals in which there is a substituent alpha to the aldehyde yielding polymerized product.

The anilines solvated in phosphotungstic acid form one phase whereas the α,β -unsaturated carbonyl compound in toluene forms another phase. The reaction occurs at

the boundary and mass transfer is achieved by stirring the reaction mixture vigorously. The reaction product quinoline also gets solvated in the catalyst phase making the easy isolation of the product. The insolubility of phosphotungstic acid in toluene minimizes polymerization of crotonaldehyde or methyl vinyl ketone.

In conclusion, we have developed a simple and general method for the synthesis of quinaldines and lepidines using safe, stable, readily available and easy to handle phosphotungstic acid. The notable advantages of this procedure are (1) operational simplicity and (2) the reaction can be carried out under thermal conditions or with microwave irradiation owing to the crystalline nature and Brønsted acidity of the catalyst.

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21. Typical procedure: (a) thermal conditions: aniline (2 mmol) was added to phosphotungstic acid (2 mmol) dissolved in 8 mL of water. To this was added crotonaldehyde (3 mmol) in 15 mL of toluene and the mixture stirred vigorously at a temperature of 100 °C for 2 h. The lower aqueous layer was separated and basified using sodium hydroxide solution and the liberated quinaldine extracted with ethyl acetate, the extract dried over anhydrous sodium sulfate, concentrated and then purified by column chromatography over silica gel eluting with a mixture of ethyl acetate/pet ether (15:85). (b) Microwave irradiation conditions: aniline (2 mmol) was adsorbed on silica gel (0.4 g) and mixed well with phosphotungstic acid (0.2 g). To this was added crotonaldehyde (3 mmol) separately adsorbed on silica gel (0.4 g) and mixed well. The mixture was then irradiated with microwaves at a power of 80% at a pulse rate of 45 s for 10 min. After completion of the reaction, the mixture was eluted with ethyl acetate, the extract dried over anhydrous sodium sulfate, concentrated and then purified by column chromatography over silica gel eluting with a mixture of ethyl acetate/pet ether (15:85). Spectral data: quinaldine, **2a**: IR (KBr): cm^{-1} . 1601, 1504, 1424, 819, 746. ^1H NMR (500 MHz, CDCl_3): δ = 2.70 (s, 3H), 7.20 (d, 1H, J = 8.6 Hz), 7.42 (m, 1H), 7.63 (m, 1H), 7.70 (d, 1H, J = 8.6 Hz), 7.96 (d, 1H, J = 8.6 Hz), 7.99 (d, 1H, J = 8.6 Hz). ^{13}C NMR (125 MHz, CDCl_3): δ = 25.46, 121.99, 126.55, 127.55, 127.59, 129.51, 136.26, 136.31, 147.85, 159.03. MS: m/z 143 (M^+).
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