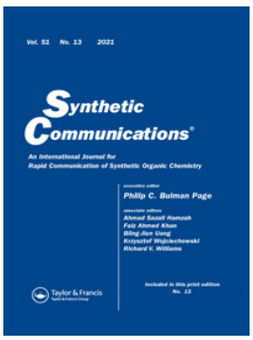

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Synthesis of novel 2-methyl-4-carboxyquinolines, the new by-products of the Doebner reaction

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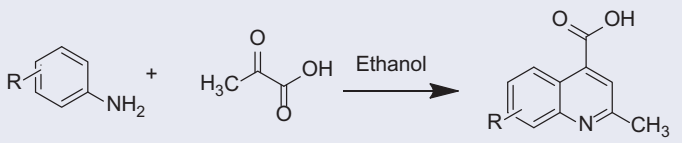
ABSTRACT

The Doebner reaction is the chemical reaction of an aniline with an aldehyde and pyruvic acid to form quinoline-4-carboxylic acids. Although Doebner reaction is a simple procedure for synthesis of 4-carboxyquinolines, which the product precipitates from the reaction mixtures with high purity, its yield is not high due to the formation of different reaction by-products. In the present study we found a new by-product (2-methylquinoline-4-carboxilic acid derivative), in Doebner reaction. We synthesized new 2-methylquinoline-4-carboxilic acid derivatives simply by stirring pyruvic acid and aromatic amine in ethanol with high purity. Generally, we found that aniline derivatives possessing electron donating groups are needed for the synthesis of 2-methylquinoline-4-carboxilic acid derivatives in ethanol. ^{1}H-NMR data of products revealed that this reaction is regioselective and ring closure occurs on the position with less steric hindrance. The order of mixing of the reactants plays a key role in determining the type of products in the Doebner reaction.

GRAPHICAL ABSTRACT



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KEYWORDS
Doebner reaction; 2-methylquinoline-4-carboxilic acid; pyruvic acid; quinoline; synthesis

Quinoline is an important scaffold for the lead compounds in drug discovery and plays a key role in the field of medicinal chemistry.[1] Currently there are many articles reporting synthesis of the quinoline derivatives for pharmaceutical activities. Interest in the synthesis of compounds possessing the quinoline scaffold has increased in recent years because of their various biological properties.[2–9] So far, a variety synthesis procedures have been described in the literatures[10–20] for the formation of this scaffold. For example, named reaction including Friedländer, Gould-Jacob, Pfitzinger, Doebner-von Miller, Skraup, and Conrad-Limpach are traditional synthesis procedures were used for the creation of the quinoline scaffold. The Doebner reaction is the chemical reaction of

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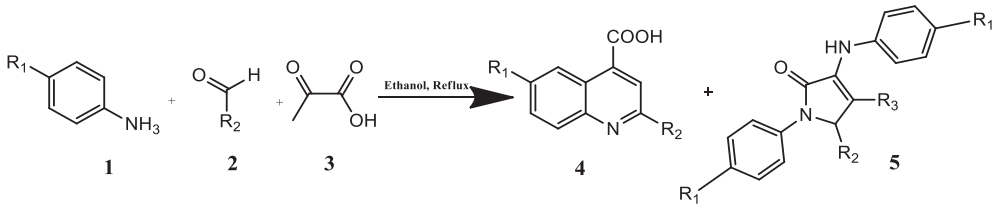
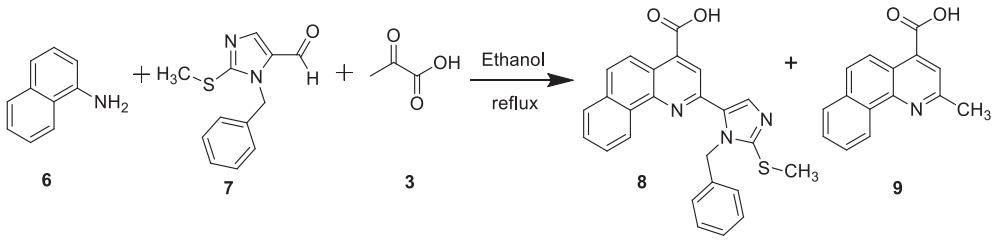


Scheme 1. The products (**4**) and the by-products (**5**) of the Doebner reaction.

an aniline with an aldehyde and pyruvic acid to form quinoline-4-carboxylic acids.[21] In 1887, Doebner reported the reaction of aromatic amines, aldehydes, and pyruvic acid to afford quinolinic acid[22] which is now known as the "Doebner reaction." The most imperative reported procedures for the synthesis of the quinoline-4-carboxylic acids involve the Pfitzinger reaction of isatin with a carbonyl compound in the presence of an appropriate base and Doebner reactions of aromatic amines, aldehydes, and pyruvic acid.[23] The Doebner reaction was initially reported by Doebner in 1887 for the synthesis of cinchoninic acid or quinolinic acid derivatives. Although Doebner reaction is a simple procedure for synthesis of 4-carboxyquinolines, which the product precipitates from the reaction mixtures with high purity, its yield is not high due to the formation of different reaction by-products. It is found that the formation of these by-products depends on defined property combinations of the respective starting materials. We discovered a new by-product (2-methyl-4-carboxyquinoline) in Doebner reaction which encouraged us to examine the reaction of pyruvic acid with different aromatic amines to synthesis of novel 2-methyl-4-carboxyquinolines.

Weber et al.[24] reported Doebner-type synthesis of quinoline from anilines, various aldehydes and pyruvic acid derivatives. They found that, the reaction yielded not only the expected substituted quinoline-4-carboxylic acids **4** but also 3-arylamino-dihydropyrrol-2-ones **5** (4 component product) (Scheme 1).

They also described a full combinatorial library including anilines possessing electron donating and withdrawing groups, aliphatic and aromatic aldehydes as well as various pyruvic acid derivatives which provided additional products with diverse structures. Recently, we synthesized various 2-aryl-4-carboxyquinolines using Doebner reaction and different benzaldehyde and aniline derivatives and pyruvic acid as the starting materials.[10–16,18–20,25] Generally, we found that aniline derivatives possessing electron donating groups are needed for synthesis of quinolines in ethanol by Doebner reaction.[20] We could not synthesize 2-aryl-4-carboxyquinolines by aniline or aniline derivatives possessing electron withdrawing groups such as *para* chloroaniline.[20] For synthesis of 2-aryl-4-carboxyquinolines possessing benzoyl group in position 4 or 6 of quinoline ring, replacing ethanol (the solvent reaction) with acetic acid led to the formation of these quinolines.[19] The quinolines which do not have any substitution in positions 5–8 of quinoline ring or possessing electron withdrawing groups can be synthesized by Pfitzinger reaction using isatin and isatins possessing electron withdrawing groups respectively.[20] In one of our ongoing research, when we used 1-benzyl-2-(methylthio)-1*H*-imidazole-5-carbaldehyde instead of benzaldehydes, the target product 2-(1-benzyl-2-(methylthio)-1*H*-imidazol-5-yl)benzo[h]quinoline-4-carboxylic acid **8** was not achieved. ^{1}H-NMR data revealed that 2-methylbenzo[h]quinoline-4-carboxylic

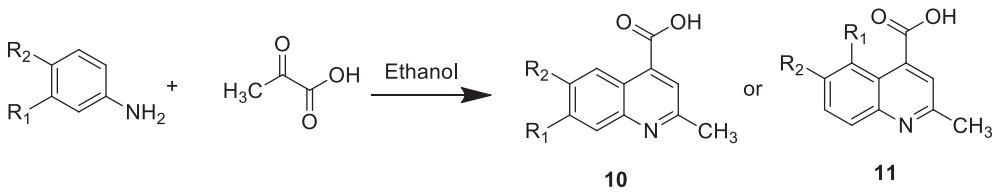


Scheme 2. synthesis of the target product 2-(1-benzyl-2-(methylthio)-1*H*-imidazol-5-yl)benzo[h]quinoline-4-carboxylic acid **8.**

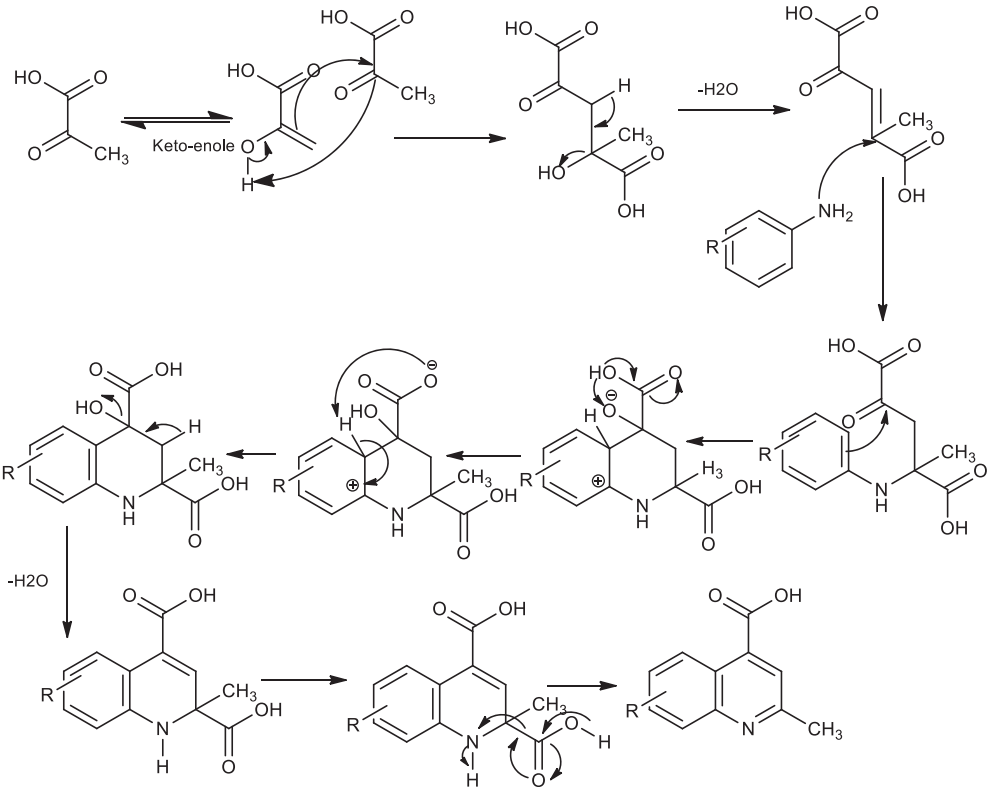
acid **9** was obtained instead. So we found a new by-product (2-methylquinoline-4-carboxilic acid derivative) in the Doebner reaction (Scheme 2).[15] For synthesis of the target product 2-(1-benzyl-2-(methylthio)-1*H*-imidazol-5-yl)benzo[h]quinoline-4-carboxylic acid **8**, at first we let pyruvic acid **3** and aldehyde **7** react, then we added aromatic amine **6**, which led to the formation of the target quinoline **8**. So we can conclude that the order of mixing of the reactants plays a key role in determining the type of product in the Doebner reaction.

This finding encouraged us to examine the synthesis of 2-methylquinoline-4-carboxylic acids using aromatic amines and pyruvic acid in ethanol under reflux conditions. However, synthesis of some of the 2-methylquinoline-4-carboxylic acids using aromatic amines and pyruvic acid were reported in the old literatures but they are not available or the authors did not describe the details of their synthesis[26,27] or reported other products.[28,29] 2-Methylquinoline-4-carboxylic acids are widely used in organic synthesis for the preparation of various derivatives possessing high biological activity.[30–39] These compounds are usually obtained by the Pfitzinger reaction, by heating a mixture of substituted isatin with acetone in the presence of alkali. Some researcher reported low yields for this reaction. Apparently, the low yields of 2-methylquinoline-4-carboxylic acids prepared by addition of alkali to a mixture of isatin derivatives with acetone is clarified by a considerable influence of the side reaction occurring by addition of acetone to isatin, which heads opening of the isatin ring. The resulting unsaturated intermediate is probably undergoing tarring at high temperature, thus, decreasing the yield of the target product.[39]

As we found 2-methylquinoline-4-carboxylic acids as the by-product of Doebner reaction, we stirred different aniline derivatives with pyruvic acid in ethanol under reflux conditions and we obtained pure 2-methylquinoline-4-carboxylic acids, then we let aniline derivatives with pyruvic acid react at room temperature which led to precipitate highly pure target product, so we reported the simple, soft, and efficient procedure for synthesis of 2-methylquinoline-4-carboxylic acid derivatives. These compounds are usually obtained by the Pfitzinger reaction, i.e., by heating a mixture of substituted isatin with acetone in the presence of alkali and for synthesis of the target compounds by the Pfitzinger reaction, we need special isatin which may not be available and we must synthesize them, but by the procedure we reported, we just need aromatic amines which are usually available. However, we could not synthesize 2-methyl-4-carboxyquinolines by aniline or aniline derivatives possessing electron withdrawing group such as para chloroaniline. Generally, we found that aniline derivatives possessing electron donating groups are needed for synthesis of 2-methyl-4-carboxyquinolines in ethanol. We proposed the mechanism for the



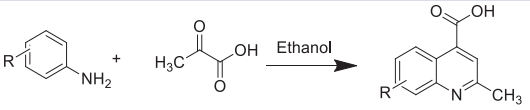
Scheme 3. Two possible cyclization pathways in the synthesis of 2-methylquinoline-4-carboxylic acid.

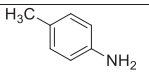
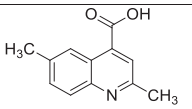
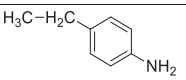
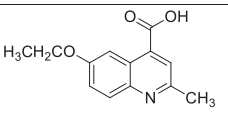
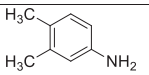
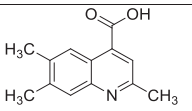
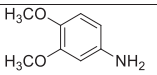
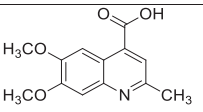
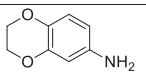
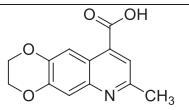
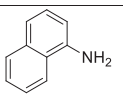
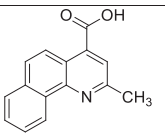
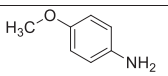
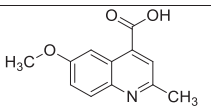
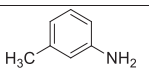
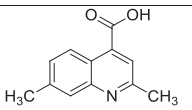
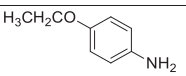
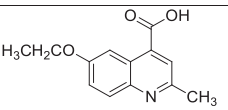
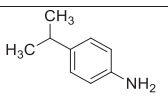
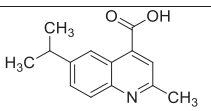
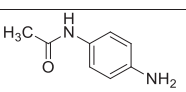
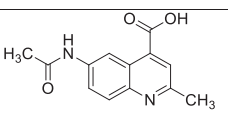


Scheme. 4. The proposed mechanism for formation of 2-methyl-4-carboxyquinoline using aromatic amines and pyruvic acid.

formation of 2-methylquinoline-4-carboxylic acid derivatives (Scheme 3)[41] which it is not reported in the literatures describing the mechanism of reaction between pyruvic acid and aromatic amines.[27–29] According to the proposed mechanism, the amount of the pyruvic acid was used stoichiometrically twice that of the aromatic amine. ^{1}H-NMR data of products presented in entries 3,4, 5, and 8 of Table 1, revealed that this reaction is regioseletive. As shown in Scheme 3, pyruvic acid and aromatic amine were stirred in ethanol to obtain quinolines. In this condition, two cyclization ways were probable (Scheme 3); linear (2-methyl-6,7-disubstutedquinolines, **10**) or angular (2-methyl-5,6-disubstutedquinolines, **11**). The ^{1}H NMR data showed three singlet signal for the product of entry 3,4 and 5 and confirmed that the only product of this reaction is compounds **10**, however, the angular isomer **11** was not obtained, and this finding can be due to the steric factors.

Table 1. Starting materials and products, substituted anilines (a) and 2-methyl-4-carboxyquinoline (b).



Entry	Compound	Anilines (a)	2-Methyl-4-carboxyquinolines(b)	Ref
1	**10a**			(40)
2	**10b**			
3	**10c**			
4	**10d**			
5	**10e**			
6	**10f**			(41)
7	**10g**			(26)
8	**10h**			
9	**10i**			
10	**10j**			
11	**10k**			

General procedure for preparation of 2-methylquinoline-4-carboxilic acid derivatives

As elucidated in Table 1, various aromatic amines (1 mmol) and pyruvic acid (2 mmol) were stirred in ethanol (10 ml) until the precipitate was formed (2–5 h). The obtained precipitate was filtered and washed with ethanol and recrystallized from ethanol to obtain quinolines **10a**–**10k**. The purity of all the products was determined by thin layer chromatography using several solvent systems of different polarity. All compounds were pure and stable.

6,7-Dimethoxy-2-methylquinoline-4-carboxylic acid (10d)

Cream solid; yield: 67%; mp: 280–285 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.65 (s, 3H, CH3). ^{13}C NMR (76 MHz, DMSO) δ 168.38, 156.11, 152.44, 150.18, 146.22, 134.14, 121.24, 118.98, 108.19, 103.73, 56.10, 55.89, 24.73. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67; Found: C, 63.21; H, 5.41; N, 5.69.

7-Methyl-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline-9-carboxylic acid (10e)

Off white solid; yield: 60%; mp: 300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.11 (s, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 7.38 (s, 1H), 4.40 (s, 4H, OCH_2), 2.64 (s, 3H, CH_3). ^{13}C NMR (76 MHz, DMSO) δ 168.05, 156.86, 147.19, 145.13, 145.01, 134.62, 121.82, 119.17, 113.24, 110.46, 64.77, 64.66, 24.72. Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.71; H, 4.51; N, 5.62.

In conclusion in the present study, we found a new by-product (2-methylquinoline-4-carboxilic acid derivative), in the Doebner reaction. The order of mixing of the reactants plays a key role in determining the type of products in the Doebner reaction. We synthesized new 2-methylquinoline-4-carboxilic acid derivatives by stirring pyruvic acid and aromatic amine in ethanol.[1]H-NMR data of products revealed that this reaction is regioseletive and ring closure occurs on the position with less steric hindrance.

Full experimental detail, ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

Disclosure statement

The authors declare that there is no conflict of interests.

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