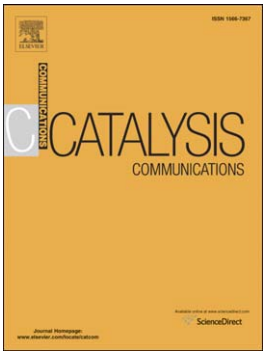

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Toward the synthesis of 6-hydroxyquinoline starting from glycerol *via* improved microwave-assisted modified Skraup reaction

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Abstract

Efficient modified Skraup reaction and Bamberger rearrangment in neat water was developed using nitrobenzene and inexpensive, abundant and environmentally-friendly glycerol under microwave irradiation conditions to furnish regioselectively the 6-hydroxyquinoline. The target compound was obtained in 77% yield *via* efficient domino reaction with an "one pot eleven steps".

Keywords

glycerol – Skraup – Bamberger – aqueous catalysis – 6-hydroxyquinoline – microwaves – domino reaction

Highlights

Efficient modified Skraup reaction and Bamberger rearrangement

Modified Skraup reaction without As_2O_5

Synthesis of 6-hydroxyquinoline under microwave irradiation conditions

Synthesis of 6-hydroxyquinoline *via* a domino reaction

1. Introduction

Quinoline derivatives represent an important class of heterocycles. The quinoline ring system occurs in various natural products, especially in alkaloids such as quinine for the treatment of malaria [1] and thereafter in many synthetic pharmaceutical agents such as chloroquine and mefloquine. In addition, the quinoline skeleton is often used for the design of many ligands [2] and functional material [3]. Among the quinoline derivatives, 6-hydroxyquinoline (**5**) is a starting heterocycle for pharmaceutical research and electronic material [4].

The structural core of quinoline has generally been synthesized by various conventional reactions such as Skraup reaction [5], Doebner-Miller reaction [6], Friedlander reaction [7], Pfitzinger reaction [8], Conrad-Limpach reaction [9], Combes reaction [10]. The major advantages of the Skraup reaction are its simple experimental protocol and the use of glycerol (**1**) as the main byproduct of the biodiesel industry. Indeed, starting from glycerol (**1**), aniline analogues, strong acid and various oxidants, the corresponding quinoline derivative is obtained in medium yield. However, several drawbacks are observed such as harsch reaction conditions, requiring high temperature (>200°C) and highly acidic conditions resulting in lower yields of products due to the tedious isolation from complex reaction mixtures. It is also noted that, using the Skraup reaction, only the benzene ring of the quinoline may be substituted. Accordingly, the substitution at the 5-, 6-, 7- and 8- positions depends on the choice of the substituted aniline used as starting material.

Due to recent efforts in developing green chemistry and sustainable development for academic and industrial research, chemists have recently established catalytic reactions based on renewable resources, atom economy, less hazardous chemical syntheses, safer solvents, auxiliaries and alternative technologies such as microwave irradiations. The chemical industry demands short reaction time, high selectivity and these objectives can be obtained *via* microwave irradiation as a practical alternative to conventional heating. In this respect, the microwave-assisted Skraup reaction was developed for the synthesis of quinoline analogues using 2,6-diaminotoluene, glycerol, arsenic(V) oxide and sulfuric acid at 132°C for 33 minutes. The target heterocycle was prepared in 32% yield [11].

Using the Skraup methodology, the 6-hydroxyquinoline (**5**) was obtained starting from the 4-hydroxyaniline (**6**) in presence of glycerol (**1**) in acidic media [12]. H_2SO_4 50%, 4-hydroxyaniline (**6**), glycerol (**1**) and iodine were mixed at 150°C under 1.5 bar for 8 hours and furnished the heterocycle **5** in 82% yield. It was notable that the most classical protocol for the synthesis of 6-hydroxyquinoline (**5**) did not build the quinoline core but started from 6-substituted quinoline having either a chlorine atom [13], a methoxy group [14] or a benzyl

group [15]. In 2010, Cho et coll. described the synthesis of various quinoline analogues by reduction of the nitroarene followed by propanol group transfer from tris(3-hydroxypropyl)-amine and cyclization under heterogeneous Pd-C catalysis [16]. For example, the 6-hydroxyquinoline (**5**) was obtained in 66% yield starting from 4-nitrophenol (**7**). In order to provide a protocol for the synthesis of 6-hydroxyquinoline (**5**) according to the principles of green chemistry and sustainable development, modified Skraup reaction was examined and toxic reagents such as As_2O_5 were removed.

2. Experimental

2.1 General

All reactants were obtained from Acros Organics and were used as received without further purification. Solvents were purchased from Carlo Erba. Chromatography was performed on a neutral silica gel.

Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. Monowave300 (Anton Paar, Austria) is a mono-mode cavity with a microwave power delivery system ranging from 0 to 850 W. The temperatures of the reactions were mainly monitored *via* contactless infrared pyrometer, which was calibrated in control experiments with a fibre-optic contact thermometer. Reaction time described corresponds to 40 minutes (a heating ramp of 7°C.min^{-1} for 30 minutes then 220°C for 10 minutes). Sealed vessels and magnetic stir bar inside the vessel were used. Temperature and power profiles were monitored in both cases through the software provided by the manufacturer.

2.2. Characterization

NMR spectra of products were recorded on a Bruker instrument operating at 400.13 MHz for proton and 100.62 MHz for carbon. The qualitative and quantitative analysis of the reactants and products was performed by liquid chromatography. Products were identified by a comparison with authentic samples.

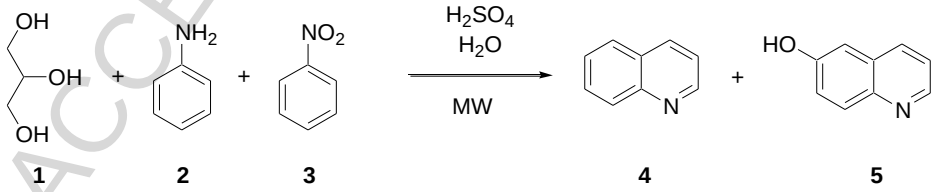
2.3. Typical procedure for the modified Skraup reaction

A 30 mL sealed vessel was charged with nitrobenzene (**3**, 10 mmol), glycerol (**1**, 40 mmol, 4.0 eq), H_2SO_4 (30 mmol, 3 eq) in water (7.4 mL). The mixture was irradiated with a power high enough to reach the predicted temperature with a heating ramp of 7°C.min^{-1}, then 220°C for 10 minutes. After cooling at room temperature, pH was adjusted at 8-9 by addition of

NaOH and the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (cyclohexane/EtAc, 1:1, v/v) on silica gel yielding the 6-hydroxyquinoline (**5**, 1.12 g, 77%).

3. Results and discussion

In the first set of experiments, the most toxic and poisonous reagents like arsenic oxide used in the Skraup reaction were removed and water was added as green solvent. In this regards, the reaction of glycerol (**1**) (4 equiv) with aniline (**2**) (0.5 equiv) and nitrobenzene (**3**) (0.5 equiv) in presence of sulfuric acid (3 equiv) was carried out as a model reaction in sole water at 220°C under microwave irradiations (Scheme 1). The mixture was irradiated with a power high enough to reach the predicted temperature with a heating ramp of 7°C.min^{-1}, then 220°C for 10 minutes. In the present work, this microwave irradiation protocol was always used. In our hands, a mixture of two quinolines was obtained, the parent quinoline (**4**) in 42% yield and traces of 6-hydroquinoline (**5**) (Scheme 1). The presence of traces of 6-hydroxyquinoline (**5**) is interesting in two titles. In a first part, 4-hydroxyaniline (**6**), usually used as starting product for the preparation of heterocycle **5** [12], was not added to the reaction. In the second part, in the classical Skraup reaction, nitrobenzene (**3**) was used as oxidant and did not allow the synthesis of 6-hydroxyquinoline (**5**).



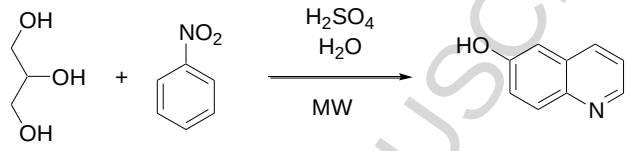
Scheme 1. Synthesis of quinoline and 6-hydroxyquinoline.

As a first conclusion, the substitution of the benzene ring at the 6- position by a hydroxyl group was linked either to the presence of nitrobenzene and/or the experimental conditions. The Skraup reaction was tested without aniline (**2**). In our hands, the reaction of glycerol (**1**) (4 equiv) with nitrobenzene (**3**) (1 equiv) in presence of sulfuric acid (3 equiv) furnished regioselectively the 6-hydroxyquinoline (**5**) in 60% without traces of quinoline (**4**) (Table 1, entry 1). Lowering the temperature from 220°C to 150°C decreased the yield of the target 6-hydroxyquinoline (**5**) (Table 1). Less than 200°C, the formation of acrolein from glycerol (**1**)

was not efficient and did not permit the formation of the target heterocycle **5** in good yield. Considering the yield obtained at 220°C, this temperature was chosen.

Table 1

Variation of temperature for the modified Skraup reaction starting from glycerol (**1**) and nitrobenzene (**3**) in water under microwave irradiations.[a]



1 **3** **5**

Entry	Temp. (°C)	Yield (%)
1	220	60
2	210	57
3	200	30
4	190	17
5	175	3
6	150	1

[a] Reaction conditions: **1** (40 mmol), **3** (10 mmol), H_2SO_4 (30 mmol), water (3.70 mL), 40 min under microwave activation (heating ramp = 7°C.min^{-1} then predicted temperature for 10 min).

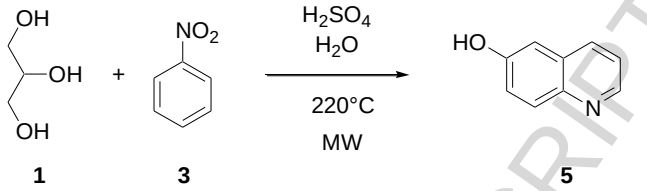
In view of these preliminary results, the use of nitrobenzene (**3**) as the sole source of aromatic ring assumed that (i) the nitro group was reduced in our experimental conditions; (ii) the hydrogen atom in para position of the arene **3** was substituted by an hydroxyl group.

In search of a more efficient catalyst, the next step consisted of examining different acids such as $FeCl_3$, $H_2SO_4/FeCl_3$, $FeCl_3$/AcOH, $Fe_2(SO_4)_3$, $H_2SO_4/Fe_2(SO_4)_3$ and by varying their concentration (from 1.0 equiv to 5 equiv) using the experimental conditions described above (Table 1, entry 1). Even though all the acid or mixture of acids promoted the formation of 6-hydroxyquinoline (**5**), none of these acids was as good as H_2SO_4 (3 equiv).

Starting from the nitrobenzene (**3**), the formation of 6-hydroxyquinoline (**5**) may be due to the presence of water as solvent as mentioned above. The concentration of the starting materials: glycerol (**1**) and nitroarene **3** in water has been modulated to investigate the best ratio (Table 2). The presence of added water was not required to obtain the 6-hydroxyquinoline (**5**) due to the continuous formation of water by double dehydratation of glycerol (**1**) to acrolein (Table 2, entry 1). In this case, the yield of heterocycle 5 was low (25%). However, the yields of the 6-hydroxyquinoline (**5**) were significantly improved when water was added as solvent (Table 2, entries 2-20). In our hands, the higher yield was obtained by mixing glycerol (**1**) (4 equiv) with nitrobenzene (**3**) (1 equiv) in presence of sulfuric acid (3 equiv) in water (7.5 mL, 41.7 equiv).

Table 2

Variation of the concentration of the starting materials **1** and **3** in water for the modified Skraup reaction under microwave irradiations.[a]



1 **3** **5**

Entry	H_2O (mL)	H_2O (equiv)	Yield[a] (%)

1	0	0	25
2	0.25	1.4	15
3	0.50	2.8	16
3	0.75	4.2	20
4	1.00	5.6	30
5	1.25	6.9	33
6	1.50	8.3	38
7	1.75	9.7	42
8	2.00	11.1	45
9	2.50	13.9	53
10	3.00	16.7	57
11	3.50	19.4	60
12	4.00	22.2	62
13	4.50	25.0	65
14	5.0	27.8	68
15	5.5	30.5	68
16	6.0	33.3	71
17	6.5	36.1	75
18	7.0	38.9	75
19	7.5	41.7	77
20	8.0	44.4	77

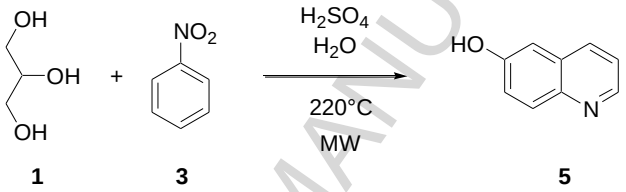
[a] Reaction conditions: **1** (40 mmol), **3** (10 mmol), H_2SO_4 (30 mmol), water (0-8.0 mL), 40 min under microwave activation (heating ramp = 7°C.min^{-1} then predicted temperature for 10 min).

In order to reduce the quantity of reagents, the concentration of glycerol was decreased (Table 3). In our hands, the modified Skraup reaction using glycerol (**1**) (3 equiv) with nitrobenzene

(**3**) (1 equiv) in presence of sulfuric acid (3 equiv) in water (0-5.5 mL) furnished moderate yield. The optimal one was 41% yield using 4.5 mL (25 equiv) of water. It seems clear that the limiting step of the modified Skraup reaction is the formation of acrolein and the presence of a large amount of glycerol is required (4 equiv *vs* 3 equiv).

Table 3

Variation of the concentration of the starting materials **1** and **3** in water for the modified Skraup reaction under microwave irradiations.[a]



1 **3** **5**

Entry	H_2O (mL)	H_2O (equiv)	Yield[a] (%)
1	0	0	10
2	1.0	5.6	25
3	1.5	8.3	29
4	2.0	11.1	32
5	2.5	13.9	34
6	3.0	16.7	34
7	3.5	19.4	38
8	4.0	22.2	40
9	4.5	25.0	41
10	5.0	27.8	40
11	5.5	30.5	41

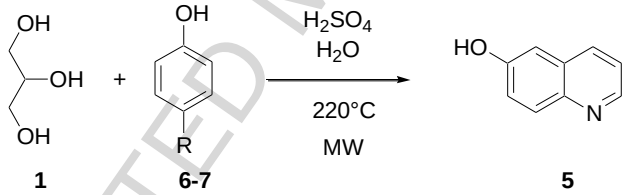
[a] Reaction conditions: **1** (30 mmol), **3** (10 mmol), H_2SO_4 (30 mmol), water (0-5.5 mL), 40 min under microwave activation (heating ramp = 7°C.min^{-1} then predicted temperature for 10 min).

The same experiment was applied under conventional heating for 24 hours yielding only traces of compound **5** (<3% yield). In our hands, only the MW irradiation permitted to furnish the target compound in significant yield.

Using the optimized method (Table 2, entry 19), 4-nitrophenol (**7**) and 4-hydroxyaniline (**6**) as aromatic sources were tested. Starting from 4-nitrophenol (**7**), the 6-hydroxyquinoline (**5**) was obtained in 55% yield while from 4-hydroxyaniline (**6**) the target heterocycle **5** was obtained in 27% yield (Table 4). In our case, the use of nitrobenzene (**3**) as starting material provided the 6-hydroxyquinoline (**5**) with the best performance (77% yield).

Table 4

Variation of the nitroarenes for the modified Skraup reaction in water under microwave irradiations.[a]



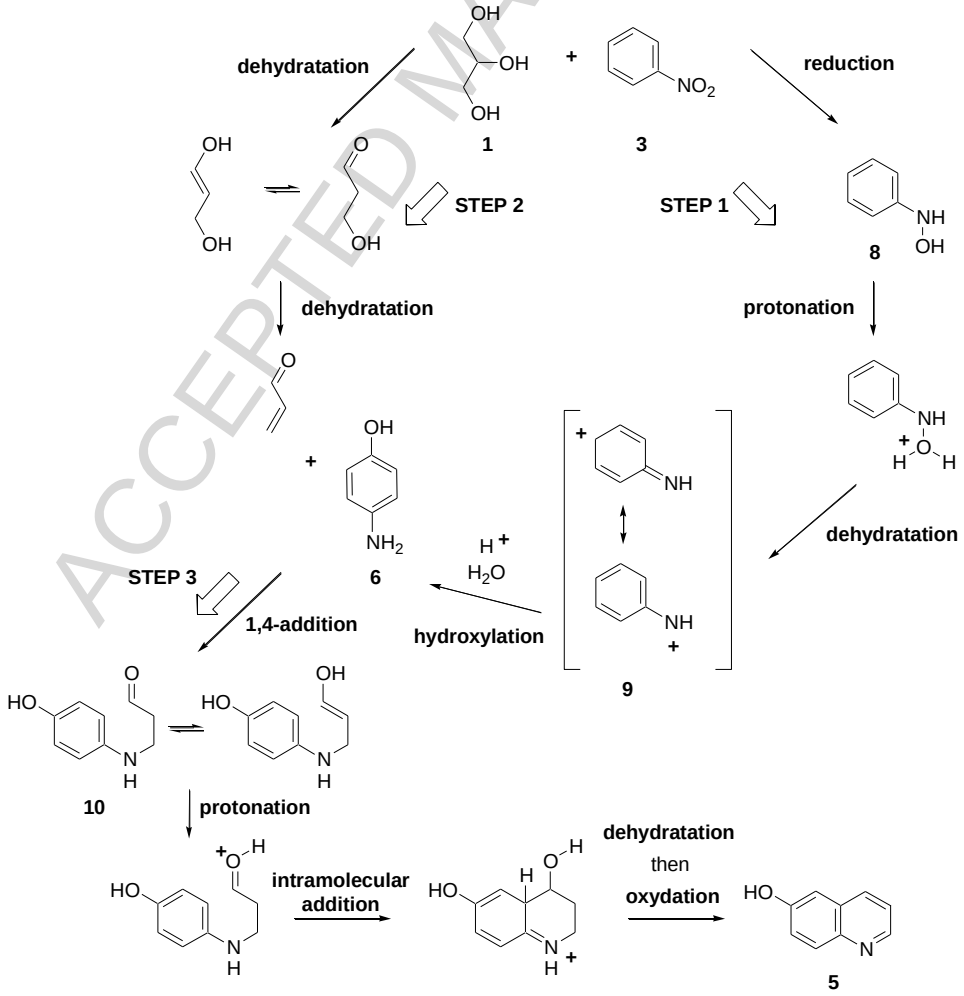
1 **6-7** **5**

Entry	Nitroarenes	R	Yield[a] (%)
1	**6**	NH_2	27
2	**7**	NO_2	55

[a] Reaction conditions: **1** (30 mmol), **6-7** (10 mmol), H_2SO_4 (30 mmol), water (0-7.36 mL), 40 min under microwave activation (heating ramp = 7°C.min^{-1} then predicted temperature for 10 min).

One plausible mechanism for the modified Skraup reaction was envisaged and might involve the formation *N*-hydroxylaniline (**8**). It was notable that this one permitted to afford industrially the 4-hydroxyaniline (**6**) *via* the Bamberger reaction. In our conditions, the reduction of the nitrobenzene (**3**) in the presence of glycerol (**1**) furnished the *N*-hydroxylaniline (**8**). After *O*-protonated of compound **8**, elimination of a molecule of water afforded the nitrenium ion **9**. Intermediate **9** may then react with a molecule of water to

furnish the 4-hydroxyaniline (**6**) (Scheme 2, step 1). The formation of acrolein from glycerol (**1**) by double dehydratation in acidic conditions is a known mechanism (Scheme 2, step 2). The regioselective 1,4-addition of 4-hydroxyaniline (**6**) to acrolein afforded the corresponding aldehyde **10**. After protonation of aldehyde **10**, the dehydrative ring closure obtained in two steps by intramolecular addition and dehydratation was followed by oxidation of the aromatic ring conducted to the final heterocycle **5** (Scheme 1, step 3). The proposed mechanism permitted to explain the synthesis of 6-hydroquinoline (**5**) *via* modified Skraup reaction in an "one pot eleven steps" is a typical domino reaction. It was noteworthy that an increase of water led to an increase in the 6-hydroxyquinoline (**5**) yield (Tables 2 and 3). It seemed reasonable that this effect was due to the hydroxylation step from compound **9** to the 4-hydroxyaniline (**6**).



Scheme 2. Plausible mechanism for the synthesis of 6-hydroxyquinoline.

4. Conclusion

In summary, the classical Skraup reaction was modified to obtain the 6-hydroxyquinoline in 77% yield starting from nitrobenzene as sole source of aromatic compound. From the view point of green chemistry, the toxic reagents like arsenic(V) oxide was removed, water was used as green solvent and alternative microwave irradiations were developed. Our optimization furnished one efficient domino reaction with an "one pot eleven steps" using only glycerol, nitrobenzene, sulphuric acid and water *via* modified Skraup reaction and Bamberger rearrangement. This process permitted: (i) the reduction of nitrobenzene to 4-hydroxyaniline *via* the successive formation of *N*-hydroxylaniline and aromatic nucleophilic substitution by elimination – addition; (ii) the double dehydratation of glycerol to acrolein; (iii) the addition of 4-hydroxyaniline to acrolein. To the best of our knowledge, this is the first time that the 6-hydroxyquinoline has been obtained under such green conditions.

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Graphical abstract