Catalysis Communications 44 (2014) 15–18

Contents lists available at ScienceDirect

Catalysis Communications

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

Short Communication

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

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ARTICLE INFO

Article history:
Received 10 April 2013
Received in revised form 30 May 2013
Accepted 10 July 2013
Available online 21 July 2013

Keywords:
Glycerol
Skraup
Bamberger
Aqueous catalysis
6-hydroxyquinoline
Microwaves
Domino reaction

ABSTRACT

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

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], and 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 analogs, strong acid and various oxidants, the corresponding quinoline derivative is obtained in medium yield. However, several drawbacks are observed such as harsh 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 and 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 analogs using 2,6-diaminotoluene, glycerol, arsenic(V) oxide and sulfuric acid at 132 °C for 33 min. 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 h 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 al. described the synthesis of various quinoline analogs by reduction of the nitroarene followed by propanol group transfer from tris(3-hydroxypropyl)-amine and cyclization under heterogeneous

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1566-7367/$ – see front matter
http://dx.doi.org/10.1016/j.catcom.2013.07.029

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 fiber-optic contact thermometer. Described reaction time corresponds to 40 min (a heating ramp of 7 °C · min^{-1} for 30 min then 220 °C for 10 min). 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 chromatograph. 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 min. 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 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatograph (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 min. 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 the 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**).

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 the 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). With 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.

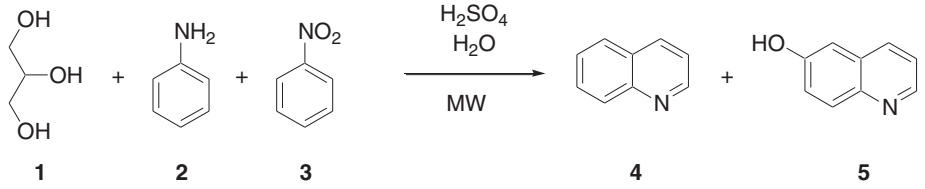
In view of these preliminary results, the use of nitrobenzene (**3**) as the sole source of aromatic ring assumed that (i) the nitro group was reduced in our experimental conditions; and (ii) the hydrogen atom in para position of the arene **3** was substituted by the hydroxyl group.

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 the presence of sulfuric acid (3 equiv) in water (7.5 mL, 41.7 equiv).

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 the 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).

The same experiment was applied under conventional heating for 24 h yielding only traces of compound **5** (<3% yield). In our hands,



Scheme 1. Synthesis of quinoline and 6-hydroxyquinoline.