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# APPLICATION OF SCHOTTEN-BAUMANN REACTION: SYNTHESIS OF SOME TETRAHYDROQUINOLINE-3-CARBOHYDRAZIDE DERIVATIVES.

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**Abstract:**

A facile and efficient synthetic route to polyhydroquinolines has been developed via four-component condensation reactions of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of organocatalysts (Guanidine hydrochloride) catalyst in ethanol at room temperature through Hantzsch reaction. Simple work-up procedure, environmentally friendly, inexpensive and non-toxic catalyst, shorter reaction times along with excellent product yields is the significant features of this practical method. Reaction continues with addition of hydrazine hydrate to obtain carbohydrazide by removing ester linkage. Finally, carbohydrazide derivatives were synthesized using Schotten-Baumann reaction.

**Keywords:**
Organocatalysts, Hantzsch reaction, Schotten-Baumann reaction, Carbohydrazide derivatives.

## Introduction:

1, 4-dihydroquinolin-5(6H)-one is a fertile source of biologically important molecules possessing various important pharmacological properties such as calcium channel antagonist[1], VEGFR-2 inhibitors[2], Immunomodulator[3], antiproliferative[4], cyclooxygenase-2 inhibitors [5], Antileishmania[6], HMG-CoA Reductase Inhibitors (antidiabetic agents)[7], Antimycobacterium[8], anti-HIV(modulators of HIV transcription)[9] and in the Potential Treatment of Protozoal and Retroviral Co-infections[10]. DPH is also useful in the treatment of myotonia in myotonic dystrophy as exemplified by therapeutic agents such as Nifedipine[11]. Thus, there is a need to discovere milder and more practicable route for the synthesis of such dihydropyridines continues to create a centre of attention of researcher.

In 1882, Arthur Hantzsch reported first synthesis of symmetrically substituted 1,4-dihydropyridines by the one-pot, four component condensation of two molecules of ethyl acetoacetate, aromatic aldehyde and ammonia. The standard Hantzsch procedure does not need the intervention of any additive or reagent and the reaction was originally conducted either in acetic acid or at reflux in alcohol for condensation products. Replacement of ammonia by ammonium acetate allowed the efficient synthesis of Hantzsch compounds in aqueous medium as well as under solvent free conditions[12]. Significant rate and yield enhancements were also reported for Hantzsch reaction carried out under microwave irradiation [13, 14] and ultrasonication [15]. The utilization of cyclic 1,3-diketone in Hantzsch reaction for the

synthesis of polyhydroquinoline is recently demonstrated by using molecular iodine [16], $SiO_2/NaHSO_4$ [17], Tungsto-phosporic acid[18], Gallium (III) Chloride[19], Ceric Ammonium Nitrate (CAN)[20], Nanoporous Acid[21], Enneamolybdomanganate(IV)[22], Ionic liquid [23, 24], Triphenylphosphine[25], expensive metal triflates, $Yb(OTf)_3$ [26] and under aqueous conditions [27, 28]. Each of the above methods for Hantzsch reaction has its own merits, while some of the limitations plagued the methods of longer reaction time, difficult work-up and effluent pollution. Moreover, there is relatively limited number of reports on the synthesis of polyhydroquinoline derivatives compared to the synthesis of simple 4-substituted 1, 4-dihydropyridine nucleus. Consequently, there is scope for further work towards increased variations of the substituents in the product, mild conditions and better yields.

Because of the current thrust in the utilization of 1,3-diketones in multi-component reactions, there are various merit in developing a truly catalytic method for the formation of polyhydroquinoline via Hantzsch reaction. The mechanism of multi-component Hantzsch reaction originally involves aldol related reactions such as Knoevenagel condensation and Michael addition, the use of guanidine hydrochloride for the same reaction will be an useful and attractive modification for the same. Guanidine hydrochloride is used as an organo-catalyst for the multicomponent Hantzsch reaction under benign reaction conditions. Our results demonstrate that guanidine hydrochloride is a very effective, environmentally friendly catalyst for the four component condensations of dimedone, ethyl acetoacetate, aromatic aldehyde and ammonium acetate to form polyhydroquinoline in excellent yields.

We further modify our scheme to achieve aryl derivative of tetrahydroquinoline-3-carbohydrazide in application of Schotten-Baumann reaction. The general features of Schotten-Baumann transformations are:

- The reaction is especially well-suited for the preparation of simple amides to complex carbohydrazide.
- In the typical procedure the alcohol or ester is mixed with excess acyl halide or anhydride in the presence of aqueous sodium hydroxide or saturated aqueous sodium bicarbonate while the reaction mixture is stirred vigorously
- The order of reactivity for alcohols is: 1°>2°>3°, which means that sterically hindered secondary and tertiary alcohols are usually acylated sluggishly;
- The order of reactivity of the amines is determined by their basicity and generally the more basic amine is acylated faster.
- Aromatic acyl halides are more stable under aqueous conditions than aliphatic acyl halides, so they are more suitable for acylation under the Schotten-Baumann conditions.
- During the acylation of amines the presence of a base is crucial, since the substrate amine is rendered unreactive upon protonation by the acid by-product (the base applied must be stronger than the substrate amine).

## Experimental

### Material and Apparatus

Commercial solvents and reagents were used without further purification. The monitoring of reaction and checking of purity of the product were done using *pre-coated plates SIL G-25* and visualization using UV lamp. Melting points were taken in open capillaries using Labin Melting Point Apparatus and are uncorrected. IR spectra were recorded using KBr pellets on a Jasco FTIR V 460 + spectrometer using Diffuse Reflectance Attachment and are reported in $cm^{-1}$. $^1H$ NMR spectra were recorded on Varian Mercury YH300 (300 MHz FT NMR) spectrometer in

$CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra were recorded on Shimadzu GC-MS QP-5050 mass spectrometer (**Table 2**). Elemental analysis was performed on Flashea 1112 series equipment by Thermoelectron Corporation (**Table 1**).

**General process for synthesis involves three steps:**

**General procedure of synthesis for dihydroquinolin-5(6H)-one 2a-2c (Step I)**

A mixture of dimedone (0.1 mol), ammonium acetate (0.1 mol), ethyl acetoacetate (0.1 mol), appropriate aldehyde (4-fluorobenzaldehyde **1a** /2-chlorobenzaldehyde **1b** (0.1 mol) and salts of guanidine (0.015 mol) in catalytic amounts were taken in 10-15 ml absolute ethanol. The reaction mixture was stirred at room temperature for overnight. The reaction was monitored by TLC (*n*-hexane : ethyl acetate, 40%), upon completion the product was filtered and recrystallized with ethanol.

**General procedure for tetrahydroquinoline-3-carbohydrazide derivative 3a-3c (Step II)**

Dihydroquinolin-5(6H)-one **2a-2b** (0.1 mol) was refluxed in the isopropyl alcohol for 30-40 min in two naked RBF, reaction continues with addition excesses of hydrazine (100%). The obtained reaction mixture was reflux for 3-4 hrs. The whole reaction was monitored by TLC (*n*-hexane : ethyl acetate, 20%). Once reaction is completed excesses of hydrazine hydrate removed under reduced pressure and the residue was obtained. Recrystallization was done with methanol.

**General procedure for aryl derivative of tetrahydroquinoline-3-carbohydrazide 5a-7a, 5b-7b (Step III)**

Tetrahydroquinoline-3-carbohydrazide (0.1mol) and mixture of aqueous sodium hydroxide (10%) and dichloromethane (DCM) were taken in two naked RBF. The mixture was stirred for 20 min.; reaction continues with addition of benzoyl chlorides (benzoyl chloride (**4a**) /4-nitrobenzoyl chloride (**4b**) /4-methoxybenzoyl chloride (**4c**)) and stirred at room temperature for overnight. The progress of reaction was monitored by TLC (*n*-hexane: ethyl acetate, 70%). Upon completion, the reaction mixture was neutralized with dilute hydrochloric acid. At neutralization point solid was precipitated out. Precipitate was filtered off, followed by washing of residues with cold water to remove the excess of benzoyl chloride and dried in vacuo. Further purification was done with methanol.

**Selected spectral and physical data of products:**

**Ethyl-4-(4-fluorophenyl)-2, 7, 7-trimethyl-5-oxo-5, 6, 7, 8-tetrahydroquinoline-3-carboxylate (2a)**

IR (KBr, $cm^{-1}$): 3290, 2960, 1695, 1610, 1490, 1380, 1220, 1025, 764; 1H NMR ($CDCl_3$) δ ppm 2.30-2.32 (t, 3H), 4.09-4.11(m, 2H), 6.90-6.92 (d, 2H), 7.28-7.30 (d, 2H), 2.30 (s, 2H), 1.07 (s, 6H), 2.20 (s, 2H) 1.68 (s, 1H); MS ($M^+$+1): 315.38; Elemental Analysis (%Cal/%Found) C (70.97/70. 69), H (6.24/6.13), N (3.94/3.67).

**4-(2-chlorophenyl)-2, 7, 7-trimethyl-5-oxo-5, 6, 7, 8-tetrahydroquinoline-3-carbohydrazide (3a)**

IR (KBr,$cm^{-1}$): 3482, 3012, 1385, 1228, 1020, 745; 1H NMR ($CDCl_3$) δ ppm 4.92 (s, 2H), 8.24 (s, 1H), 6.91-6.93 (d, 2H), 7.30-7.32 (d, 2H), 2.31 (s, 2H), 1.08 (s, 6H), 2.23 (s, 2H) 1.70 (s, 1H); MS ($M^+$+1): 342.15; Elemental Analysis (%Cal/%Found) C (66.85/66.54), H (5.91/5.54), N (12.31/12.09).

**4-(4-fluorophenyl)-2, 7, 7-trimethyl-5-oxo-N'-phenyl-5, 6, 7, 8-tetrahydroquinoline-3-carbohydrazide (5a)**

IR (KBr,$cm^{-1}$): 3482, 3012, 1789, 1700, 1020, 745; 1H NMR ($CDCl_3$) δ ppm: δ 7.70 (t, 1H), 7.63-7.65 (d, 2H) 8.03-8.05 (d, 2H), 8.29 (s, 1H), 8.31 (s, 1H), 6.91-6.93 (d, 2H), 7.30-7.32 (d, 2H), 2.30 (s, 2H), 1.08 (s, 6H), 2.23 (s, 2H) 1.70 (s, 1H); MS ($M^+$+1): 446.49; Elemental Analysis (%Cal/%Found) C (70.10/69.93), H (5.43/5.32), N (9.43/9.10).

**4-(2-chlorophenyl)-2, 7, 7-trimethyl-5-oxo-N'-phenyl-5, 6, 7, 8-tetrahydroquinoline-3-carbohydrazide (5b)**

IR (KBr,$cm^{-1}$): 3489, 3066, 1785, 1700; 1H NMR ($CDCl_3$): δ 7.72 (t, 1H), 7.63-7.65 (d, 2H) 8.00-8.02 (d, 2H), 8.29 (s, 1H), 8.31 (s, 1H), 7.52-7.54 (d, 1H), 7.36-7.37 (t, 2H), 7.73-7.75(d, 1H), 2.31 (s, 2H), 1.07 (s, 6H), 2.20 (s, 2H) 1.71 (s, 1H); MS ($M^+$+1): 462.94; Elemental Analysis (%Cal/%Found) C (67.60/67.34), H (5.24/5.12), N (9.10/8.91).

**Result and Discussion:**

Different author explains the formation of dihydroquinolin-5(6H)-one from benzaldehydes, ethyl acetoacetate and ammonium acetate in presence different catalysts such as molecular iodine, $SiO_2/NaHSO_4$, Tungsto-phosporic acid, Gallium (III) Chloride, Ceric Ammonium Nitrate (CAN), Nanoporous Acid, Enneamolybdomanganate(IV), Ionic liquid, Triphenylphosphine, expensive metal triflates, $Yb(OTf)_3$ and under aqueous conditions as we mentioned earlier part of this research paper. But we found that Guanidine hydrochloride salt is better than other catalysts due to it provides mild conditions and better yields. To study catalytic activity of guanidine hydrochloride was added in different amount to see yield of end product. We started our experiment from 0.05 mol to 0.015 mol. Using 0.015 mol of catalyst increases the yield from 87% to 93 %. Further we found the application of Schotten-Baumann reaction in our synthesis. Schotten-Baumann transformations especially use for formation of amide and carbohydrazide linkages in presence of benzoyl chlorides as shown in following scheme 1.

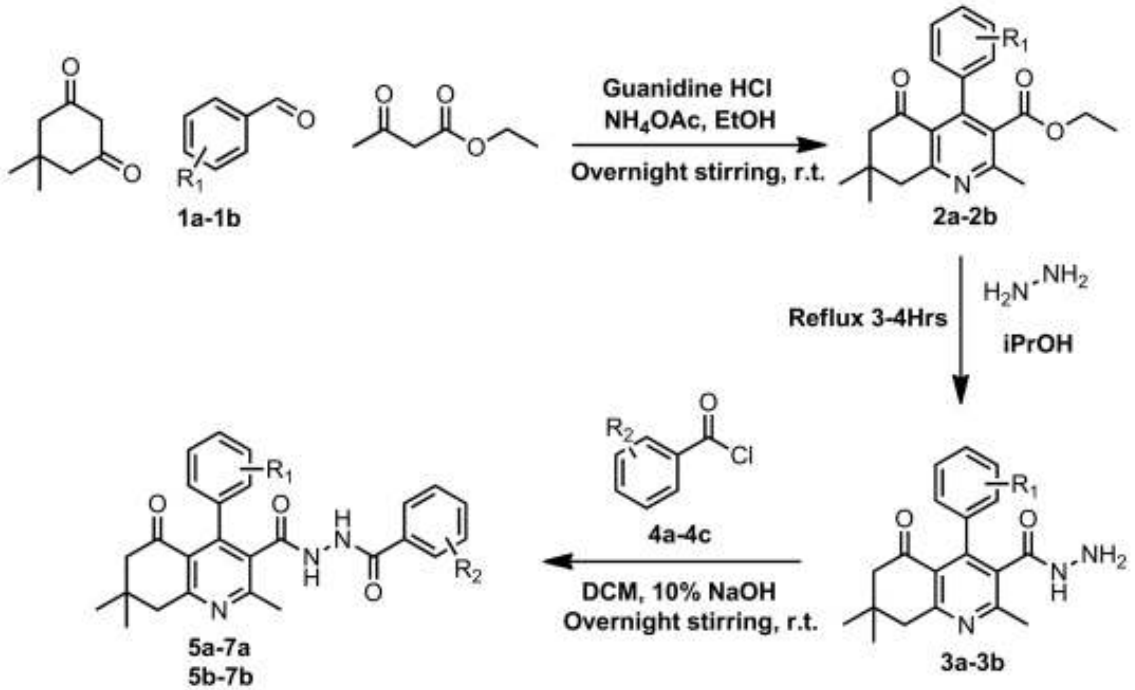


**Figure 1 Scheme for the synthesis of title compounds**

**Table no.1 Guanidine hydrochloride catalyzed synthesis of polyhydroquinoline derivatives (2a-2b) and polyhydroquinoline-3- carbohydrazide (5a-7a, 5b-7b).**

| Compound Code | Substituents | | M.P. ($^0$C) | Yield (%) | Time |
|---|---|---|---|---|---|
| | $R_1$ | $R_2$ | | | |
| **2a** | **4-F** | **-** | 182-184 | 93 | Overnight |
| **2b** | **2-Cl** | **-** | 207-209 | 92 | Overnight |
| **3a** | **4-F** | **-** | 136-138 | 78 | 90-120min |
| **3b** | **2-Cl** | **-** | 148-150 | 87 | 90-120min |
| **5a** | **4-F** | **H** | 205-207 | 92 | Overnight |
| **6a** | **2-Cl** | **4-$NO_2$** | 230-232 | 95 | Overnight |
| **7a** | **4-F** | **4-$OCH_3$** | 315-317 | 93 | Overnight |
| **5b** | **2-Cl** | **H** | 217-219 | 85 | Overnight |
| **6b** | **4-F** | **4-$NO_2$** | 282-284 | 94 | Overnight |
| **7b** | **2-Cl** | **4-$OCH_3$** | 207-209 | 95 | Overnight |

**Conclusion:**

In the end, synthesis of polyhydroquinoline-3- carbohydrazide was successfully carried out using Schotten-Baumann reaction. Application of Schotten-Baumann transformation offers significant advantages such as high yields and easy handling which makes useful method for synthesis.

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