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THE GREEN APPROACH FOR THE SYNTHESIS OF SOME HYDROQUINOLINE

DERIVATIVES COMPOUND VIA HANTZSCH REACTION

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ABSTRACT:

Since that hydroquinoline and acridine compounds serve as the fundamental building blocks for the synthesis of many different pharmaceuticals, they are among the most significant classes of chemical compounds that attract the interest of numerous researchers and pharmacologists. Therefore, in this research, The Hantzch reaction was used to prepare these types hydroquinoline and acridine derivatives of compounds, through the reaction of a number substituted benzaldehyde with demidone and α-β diketone substitutes by refluxed with sodium acetate in the presence of iodine and a 1-sulfo-4-(3- (Ferricoxide-Silicondioxide nanopowdertrioxisilyl)propyl) piperazinum-1,4-diphosphate as a catalyst to form 7,7- dimethyl -4,6,7,8-tetrahydroquinoline derivatives which is represented by compounds (1-12) or in the same way by react benzaldehyde substitutes react with demidone and 4-isopropyl cyclohexanone 1-one to form acridin derivatives represented by compounds (13 -17). All product compound are characterized using 1H-NMR spectra and the results confirmed the structures.

KEYWORDS: Nanocatalyst, Hantzsch Reaction, Dimedone, Quinoline, Quinoline derivatives.

1. INTRODUCTION:

 One of the most significant heterogeneous basic compounds with a single nitrogen atom is quinoline. Since this kind of chemical was initially isolated from coal around 1820, it can be found in natural sources *(*Kouznetsov *et al.,* 2005). It can also be extracted from oil or even from wood. It has been prepared in several ways, including chemical photocyclic reactions (Mitamura & Ogawa, 2011*;* Willumstad *et al.,* 2015) by cycling O-alkyl isocyanate compounds in the presence of iodine (Mitamura & Ogawa, 2011) and also made with titanium oxide present by converting the nitro group in aromatic compounds to an amine group (Park *et al.,* 1995). It is possible to prepare quinoline compounds by using the ionic liquid system and ultrasound *(*Hamdoon & Saleh, 2022). One of the multicomponent reactions that is crucial for the synthesis of numerous heterocyclic compounds, such as pyridine, quinoline, and acridine, is the Hantzch reaction (Sabbaghan *et al.,* 2010). In order to create hydroquinoline derivatives at room temperature and without the use of solvent, (Motokura *et al*).

 were able to produce these compounds utilizing cobalt catalyst nanoparticles *(*Motokura *et al.,* 2004*;* Sadeek *et al.,* 2023). Agrochemical applications are reported for numerous quinoline compounds *(* Tumambac *et al.,* 2004; Tong *et al.,* 2003) additionally to being employed in research on bio-organic and bio-organometallic processes *(* Safari *et al.,* 2009; Reddy *et al.,* 2012). They also play a role in the production of dyes *(*Anvar *et al.,* 2012; A. Saleh & Saleh, 2022) food colorants *(*Ranu *et al.,* 2000*;* Zhu *et al.,* 2010), pH indicators and other Organic compounds *(*Kulkarni & Török, 2010*;* Praveen *et al.,* 2010). In

additional to this they have also been used as ligands *(* Lindner *et al.,* 2018; Ali *et al.,* 2023).

2. MATERIALS AND METHODS

Instrumental part

 Melting points were uncorrected using thermal SMP30 UK melting point apparatus. Were recorded using Alpha (ATR) instrument.1 HNMR spectra were recorded using Varian Agilent 499.53MHZ instrument, DMSO as internal solvent. All chemical were supplied by sigma –Aldrich, BHD and Fluka companies.

Synthesis of Catalyst

 Thermal SMP30 UK melting point apparatus was used to determine melting points without correction. Using the Alpha (ATR) instrument. Using DMSO as the internal solvent, $¹$ HNMR</sup> spectrum was recorded using a Varian Agilent 499.53MHZ instruments and DMSO as internal solvent. Companies like Sigma-Aldrich, BHD, and Fluka provided all of the chemicals. The resultant mixture was centrifuged, decanted, washed twice with dry toluene and anhydrous Et₂O, and dried under vacuum at 90° C to yield (II). After adding 0.75 ml of piperazinume hydrochloride (0.75 mmol) to 30 ml of toluene, the mixture was refluxed for 12 hours. Centrifuging and decanting were used to separate the resulting solid, the combination was created, and it was refluxed for 12 hours. To create (III), the resulting solid was separated by centrifuging, decanting, washing with toluene, and drying at 90 C under vacuum. In order to produce nano(Fe-Si-Si-Pr-Pip-H2PO4), H3PO⁴ (0.26 ml, 5 mmol) was progressively added to (III) at room temperature, agitated for 5 hours at that temperature and for 1 hour at 60 C, and then dried under vacuum for 90^oC *(* Saleh M. Y. *et al.,* 2022).

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Figure 1: SEM image of sulfo-4-(3- (Ferricoxide-Silicondioxide nanopowder trioxisilyl) propyl) piperazinum-1,4 diphosphate.

Experimental part

Synthesis of some substituted of 7, 7- dimethyl -4,6,7,8 tetrahydroquinoline (1-6)

 In a round flask mix (0.001mol) appropriated of some different substituted benzaldehyde with (0.308g, 0.004mol) dimedone, (0.280g, 0.002mol) of ammonium acetate, (0.00015mol, 0.020g) acetylacetone compounds and again using (0.00015mol, 0.037g) of (1-sulfo-4-(3-(Carbon Nano sheet trioxisilyl) propyl) piperazinum-1, 4-diphosphate**)** in 10 ml of absolute ethanol. The mixture was refluxed. The reaction was followed by TLC (Dom: MeOH)) until the completion of the reaction. After completion of the reaction, the mixture was left to cool at room temperature. The solids were filtered, washed with cold ethanol, and dried. The crude product was recrystallized with methanol to give (1-6), Figure 2.some physical properties of this compounds are illustrated in Table 1

Figure 2: Synthesis of some substituted of 7, 7- dimethyl -4,6,7,8-tetrahydroquinoline (Saeed & Saleh, 2023).

Table 1: The physical properties of Compounds (1-6).

Time and Yield with Catalyst (Cat.), time and yield without Catalyst (I2).

Synthesis of some substituted of 7-isopropyl -3,3- dimethyl

-3,4,5,6,78,8a,9,0a-decahydroacridin -1(2H)-one(7-12)

 Mixed (0.001mol) of someone different substituted benzaldehyde with (0.308g, 0.004mol) dimedone, (0.280g, 0.002mol) of ammonium acetate, (0.020g, 0.00015mol) menthone compounds in 10 ml of absolute ethanol. The mixture

was refluxed. The reaction was followed by TLC (Dom: MeOH)) until the completion of the reaction. And other methods by using (0.00015mol, 0.037g) of (1-sulfo-4-(3-(Carbon nanosheet trioxisilyl)propyl)piperazinum-1,4-diphosphate**)** as a catalyst. After completion of the reaction, the mixture was left to cool at room temperature. The solids were filtered, washed with cold ethanol, and dried. The crude product was

recrystallized with methanol to give (7-12), Figure 3.some physical properties of this compounds are illustrated in Table 2.

Figure 3: Synthesis of some substituted of 7-isopropyl -3,3- dimethyl -3,4,5,6,78,8a,9,0a-decahydroacridin -1(2H)-one (Saied *et al.,* 2022)**.**

Comp No.	Ar-	Molecular Formula	\sim \mathbf{r} \mathbf{r} M.P. $(^{\circ}C)$	Time		Yield%		Color
				I ₂	Cat	I ₂	Cat	
$\overline{7}$	OCH ₃	379.54	199-201	6h	1.30h	53	8 8	Brown
8	NO ₂	394.52	184-185	5.30h	1.15h	44	8 6	Orang
9		393.53	175-177	5.30h	55 _{min}	61	9 $\mathbf{1}$	Dark brown
10	CH ₃	363.55	212-214	6h	1.20h	56	8 3	Brown
11	CH ₃	363.55	227-229	6h	1.25h	58	8 3	Brown
12	Br	428.41	190-191	7.40h	1.45h	47	9 $\overline{0}$	Brown

Table 2: The physical properties of Compounds(7-12).

*Time and Yield with Catalyst (Cat.), time

3. RESULT AND DISCUSSION

 The provided text is an abstract and a partial excerpt from a research paper discussing the green synthesis of heterocyclic compounds, specifically hydroquinoline and acridine derivatives, using the Hantzsch reaction was The reaction involves the use of substituted benzaldehyde, dimedone, α-β diketone, and other reagents, catalyzed by a novel nanocatalyst. The process is notable for being a more environmentally friendly approach to producing these compounds, which have applications in pharmaceuticals, dyes, food colorants, pH indicators, and other organic compounds. In figure 1, the image shows a magnetic catalytic material that has been synthesized, consisting of a core of magnetic iron oxide, coated with a silica layer, with additional functional groups contributing to its catalytic performance. This is an image captured using a Scanning Electron Microscope (SEM), which shows the surface details of a sample. According to the information provided below the image, the sample has been magnified 50,000 times, and the field of view is approximately 4.15 micrometers. These details suggest a complex and irregular surface structure.

 Visually, the surface structure appears to be layered or clustered, which may indicate that the material has a large surface area, beneficial for chemical reactions in catalytic applications.

Physical Properties of Compounds (1-6) and (7-12): From the data presented in Tables 1 and 2, several trends and observations can be noted regarding the melting points, yields, and colors of the synthesized compounds.

 The melting points for compounds 1-6 range from (167- 213)°C, and for compounds 7-12, they range from (175-229)°C. The melting points of compounds increase as the molecular weight increases, but this is not strictly linear. For example, compound 6 has a molecular weight of 388.31 g/mol but a lower melting point (177-178) °C than compound 5 (M.P. 212-213°C), despite having a lower molecular weight (323.44 g/mol). This could be due to differences in the structural arrangement, intermolecular forces, or the presence of functional groups that impact crystal lattice stability.

 Reaction Times and Yields: Reactions without a catalyst (I2) take significantly longer compared to those using a catalyst. The time difference is notable in compounds 3 and 6, where reactions take 11h and 6h, respectively, without a catalyst, and significantly reduce to 2.0 h and 1.50 h with a catalyst.

The yields are also higher when using a catalyst, with increases ranging from around (25-30)%. This suggests that the catalyst plays a crucial role in both accelerating the reaction and improving the efficiency of the synthesis.

 The color of the compounds varies from pale brown to dark brown and pale red. The change in color may indicate different

degrees of conjugation in the aromatic systems or the presence of different functional groups affecting the electronic environment of the compounds.

¹H-NMR Spectral Analysis (Compounds 1-6 and 7-12): In Tables 3 and 5, the ¹H-NMR data provides information about the different chemical environments of protons in each compound. Several key trends can be noted:

 Most of the compounds exhibit signals in the range of 6.6 - 7.4 ppm, corresponding to the protons on the aromatic rings. The multiplicity of these signals (singlet, doublet, or multiplet) reflects the substitution patterns on the aromatic rings, with ortho, meta, and para relationships between substituents influencing coupling patterns.

Methoxy (OCH3) and Acetyl (CH3CO) Groups:

 Several compounds exhibit singlets around 3.6-4.9 ppm, corresponding to methoxy (OCH3) groups, and at 2.3-2.5 ppm for acetyl groups (CH3CO). The presence of these groups indicates that the aromatic rings are substituted, which can impact the electronic properties of the compounds, potentially explaining differences in reactivity and physical properties like melting points.

 The cyclic CH² groups are generally observed between 1.8- 2.1 ppm. These protons indicate the presence of cyclic structures in the backbone of the compounds, likely contributing to their stability and rigidity.

The NH proton appears as a singlet in the range of 8.9-9.2 ppm across various compounds. The consistency of this peak suggests a stable NH group across the compounds, likely involved in hydrogen bonding interactions.

¹³C-NMR Spectral Analysis (Compounds 1-6 and 7-12): The ¹³C-NMR data in Tables 4 and 6 provides insights into the carbon environments within the compounds.

Peaks in the range of 110-160 ppm correspond to aromatic carbons. The presence of multiple signals in this region indicates

complex substitution patterns on the aromatic rings, which influence the electronic properties of the compounds.

The signals around 190-196 ppm correspond to carbonyl groups, such as those in acetyl or amide functionalities. These carbonyl groups are crucial for the reactivity of the compounds, influencing both their melting points and interaction with other molecules.

 The signals around 14-30 ppm correspond to methyl (CH3) and cyclic methylene $(CH₂)$ groups, while the methoxy groups (-OCH3) are observed around 50-60 ppm. These groups are important for the solubility and overall structure of the compounds.

 Overall Trends and Observations: The use of a catalyst (Cat.) significantly reduces the reaction time and increases the yield. This catalytic effect is likely due to the catalyst facilitating the reaction mechanism, possibly by stabilizing the transition state or enhancing the electrophilicity of key intermediates.

The ¹H and ¹³C NMR data indicate that the presence of substituents like methoxy, acetyl, and cyclic groups plays a significant role in determining both the physical and spectral properties of the compounds. These groups influence the electron density on the aromatic ring, affecting chemical shifts and coupling patterns. In addition, the main bands of the carbonyl group and the NH group in the infrared spectrum appear in the following bands Carbonyl group (C=O): Appears between 1700- 1750 cm⁻¹.

 \cdot NH group (N-H): Appears between 3300-3500 cm⁻¹.

 There is a clear relationship between the molecular structure (as inferred from NMR data) and the physical properties such as melting point, color, and yield. More conjugated systems or those with electron-donating groups (e.g., methoxy) generally show lower melting and yield without Catalyst(I2)

Table 3: ¹H NMR compounds (1-6) points, potentially due to weaker intermolecular interactions in the solid state.

0.772(s, 3H), 0.961(s, 3H), 1.903(s, 4H, 2 groups CH² cyclic), 2.225(s, 3H), 2.465(s, $\begin{array}{|l|l|} \hline \text{Perf} & 0.772(\text{s}, 3\text{H}), 0.961(\text{s}, 3\text{H}), 1.903(\text{s}, 4\text{H}, 2 \text{ groups } \text{CH}_2 \text{ cyclic}), 2.225(\text{s}, 3\text{H}), 2.463(\text{H}), 4.927(\text{s}, 1\text{H}, \text{CH}), 7.360(\text{d}, 2\text{H}), 8.066(\text{d}, 2\text{H}), 9.197(\text{s}, 1\text{H}, \text{NH}). \hline \end{array}$

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Table 5: ¹H NMR compounds (7-12)

Table 6: ¹³C NMR compounds (7-12)

Figure 4: Mechanizium of synthesis catalist (*Raoof et al., 2022*)

Figure 5: Suggestion mechanizium of synthesis hydroquinoline derivatives.

Figure 6: Structures of Tetrahydroquinoline and Octahydroacridin Derivatives Synthesized via the Hantzsch Reaction

CONCLUSION

 In conclusion, the research successfully synthesized hydroquinoline and acridine derivatives using the Hantzsch reaction. Substituted benzaldehydes were reacted with demidone and α - β diketone substitutes in the presence of sodium acetate and iodine, with a specific nanopowder catalyst, to form 7,7 dimethyl-4,6,7,8-tetrahydroquinoline derivatives (compounds 1- 12). Similarly, acridine derivatives (compounds 13-17) were obtained by reacting substituted benzaldehydes with demidone and 4-isopropyl cyclohexanone under the same conditions. These compounds are significant as they serve as fundamental building blocks in the synthesis of various pharmaceuticals. Overall, the prepared catalyst enhances the speed and efficiency of the reaction, making it an essential step in the synthesis of hydroquinoline and acridine derivatives.

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Author contribution: Authors contributed equally in the study.

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