

Synthesis of some New Fused Pyrimidine Compounds

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ABSTRACT

Biginelli reaction is a one-pot reaction which is used to prepare some of fused pyrimidine (2-Amino-4-aryl-7, 7- dimethyl-1, 4, 5, 6, 7, 8-hexahydro quinazoline-5-one) (A₁₋₆) by the action of dimedone, guanidenium hydrochloride and some substituted benzaldehyde in presence of Lewis acid represented by boric acid (20% mole).

These compounds were used later as precursors to prepare a superim type of schiff bases represented by compounds (2-Amino-4-aryl-5-hydrazono-7, 7-dimethyl-1, 4, 5, 6, 7, 8-hexahydro quinazoline) (B₁₋₆).

The assigned structure of the prepared compounds was corroborated by available physical and spectral methods.

Keywords: Biginelli reaction, dimedone, guanidenium hydrochloride, schiff bases.

-2

(A₁₋₆) -5-

-8,7,6,5,4,1 -

-7,7 -

-4-

% 20)

(A₁₋₆)

.(

.(B₁₋₆)

-8,7,6,5,4,1 -

-7,7 -

-5-

-4-

-2

INTRODUCTION

Three component one-pot condensation reaction has been emerged as a useful method in organic synthesis because the combination of three components to generate a new product in a single step is extremely economical among the multicomponent reaction (Huang *et al.*, 2005; Orru and Groen, 2009; Ryabukhin *et al.*, 2010) and efficient (Sun *et al.*, 2008; Abdel hamid *et al.*, 2011).

Additionally, this type of reaction received a great deals of attention in medical chemistry for various reasons, it's put on speed, diversity and efficiency in the drug discovery process (Müller, 2011).

Biginelli reaction is an efficient one-pot multicomponent condensation reaction that is used widely in organic and medical chemistry (Bose *et al.*, 2005; Kulkarni *et al.*, 2009; Mochaddas *et al.*, 2012). Starting from aldehyde, Urea(thiourea) and β -keto ester under strongly acidic condition represented by Lewis acid to obtain the pyrimidine-2-one analogs (Kappe, 1993; Mohammadizadeh and Firoozi, 2011), which received a significant attention owing to their biological (Shutalev *et al.*, 1998; Mobinikhaledi and Kalhor, 2010) and pharmaceutical properties (Phucho *et al.*, 2009; Piqani and Zhang, 2011; Shaikh *et al.*, 2012) such as antihypertensive (Atwal *et al.*, 1989; Atwal *et al.*, 1990), antiinflammatory and antibacterial (Jadhav *et al.*, 2012; Badadhe *et al.*, 2011, Akbas *et al.*, 2010) and antimicrobial (Beena and Akelesh, 2012) were also studied depending on this type of synthesis.

Recently, dihydro pyrimidine derivatives have been considered for the development of new anticancer drugs (Heda *et al.*, 2009; Kumar *et al.*, 2009) and antimalaria drugs (Sandhu and Sandhu, 2012).

In this presentation, Biginelli reaction was used to prepare a special type of fused pyrimidine derivatives starting from 1,3- cycloketone represented by dimedone, guanidenium hydrochloride and substituted benzaldehyde in presence of boric acid (20% mole).

This reaction proceeded through conventional method to obtain compounds 2-amino-4-aryl-7, 7-dimethyl-1, 4, 5, 6, 7, 8-hexahydro quinazolin-5-one (A_{1-6}), which is then used as good synthon to prepare another type of schiff bases represented by compounds 2-amino -4-aryl-5-hydrazono-7, 7-dimethyl-1, 4, 5, 6, 7, 8- hexahydro quinazoline compounds (B_{1-6}).

EXPERIMENTAL

Melting points (M.P.) were measured on Electrothermal SMP30- Stuart melting point apparatus and were uncorrected. Infrared (FT-IR) spectra were recorded as (KBr) disk using a Bruker, FT-IR, spectrophotometer Tensor 27. Ultraviolet (U.V) spectra were performed on Shimadzu UV-visible Spectrophotometer UV-1660 PC using methanol as a solvent. Thin layer chromatography (TLC) was carried out on silica gel (120 mesh) coated plates (2x10) cm, activated for one hour at (110-120°C) before use and the plates were developed with iodine vapor.

Synthesis of 2-amino-4-aryl-7,7-dimethyl-1, 4, 5, 6, 7, 8-hexahydro quinazolin-5-one (A_{1-6}):







Method A: (Meshram *et al.*, 2012)

A mixture of dimedone (0.002 mole/0.280 gm), aromatic aldehyde (0.002 mole), guanidenium hydrochloride (0.002 mole/0.190 gm) and boric acid (20% mole) was dissolved in absolute ethanol (25 ml) in flask equipped with condenser and dry calcium chloride tube. The mixture was refluxed for (5 hrs.), cooling then poured into (50 ml) ice- water. The coloured precipitate was filtered off and washed thoroughly with water and recrystallized from ethanol-water to yield compounds (A_{1-6}). The completion of the reaction was monitored by thin layer chromatography (T.L.C), the physical and spectral data were listed in Table (1).

Method B: (Hügel, 2009; Chebanov *et al.*, 2010)

A mixture of dimedone (0.005 mole / 0.7 gm), guanidenium hydrochloride (0.005 mole /0.5gm) and aromatic aldehyde (0.005 mole) was dissolved in xylene (10 ml) and refluxed with catalytic amount of triethyl amine (T.E.A.) (0.3 ml) for (5 hrs.). Cooling and poured into (50 ml) ice- water and then extracted with water (3 x 10 ml). The organic layer was then dried and the crud gummy product was solidified with ether. Finally, the product recrystallized from ethanol to give compounds (A_{1-6}) , (Table 1).







Table 1: Physical properties and spectral data for compounds (A₁₋₆)

Comp. No.	G	M.P.(°C)	Yield (%)	R _f Value (ethyl acetate: benzene) (2:8) ratio	UV (MeOH) λ _{max} (nm)	I.R (KBr) ν (cm ⁻¹)					
						NH ₂	N-H	C=O	C=C (cycl.)	C=N (cycl.)	others
A ₁		202-204	94	0.473	236	3320	3112	1660	1624	1612	-
A ₂		190-193	67	0.169	296	3311	3228	1651	1610	1593	NO ₂ asym 1516 sym 1338
A ₃		134-136	71	0.475	262	3309	3240	1666	1604	1589	acyclic C-O-C, 1196
A ₄		85-87	69	0.283	264	3338	3140	1670	1595	1547	-
A ₅		189-191	74	0.396	260	3333	3205	1660	1602	1593	-
A ₆		193-195	67	0.339	294	3311	3168	1662	1616	1593	cyclic C-O-C, 1257

Synthesis of 2-amino-4-aryl-5-hydrazono-7, 7-dimethyl-1, 4, 5, 6, 7, 8-hexahydro quinazo- line (B₁₋₆): (Solvam *et al.*, 2010)

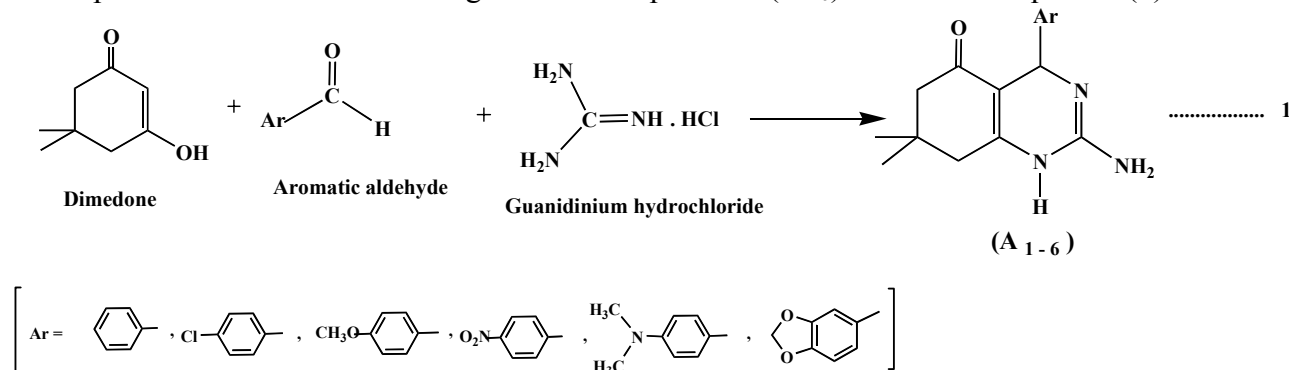
A mixture of compounds (A₁₋₆) (0.001 mole) and hydrazine hydrate (80%) (0.001 mole) was treated with anhydrous sodium acetate (0.001 mole / 0.082 gm) and glacial acetic acid (5 ml) in presence of abs. ethanol (10 ml) as solvent and then refluxed for (3 hrs.). After standing for approximately (24 hrs.) at room temperature. The precipitated product was separated by filtration and washed thoroughly with hot water to yield compounds (B₁₋₆). The progress of the reaction was followed by (T.L.C), the physical and spectral data were listed in Table (2).

Table 2: Physical properties and spectral data for compounds (B₁₋₆)

Comp. No.	G	M.P.(°C)	Yield (%)	R _f Value (ethyl acetate: benzene) (2:8) ratio	UV (MeOH) λ _{max} (nm)	I.R (KBr) ν (cm ⁻¹)					
						NH ₂	NH	C=C (cycl.)	C=N (imin)	C=N (cycl.)	others
B ₁		73-75	56	0.255	234	3330	3203	1620	1562	1493	-
B ₂		125-127	84	0.415	254	3340	3205	1612	1562	1514	NO ₂ asym 1472 sym 1342
B ₃		129-130	54	0.698	220	3373	3224	1604	1508	1454	acyclic C-O-C, 1167
B ₄		77-79	64	0.364	234	3359	3213	1620	1542	1491	-
B ₅		249-251	67	0.596	244	3263	3124	1604	1523	1479	-
B ₆		136-138	50	0.400	242	3325	3205	1620	1562	1485	cyclic C-O-C, 1230

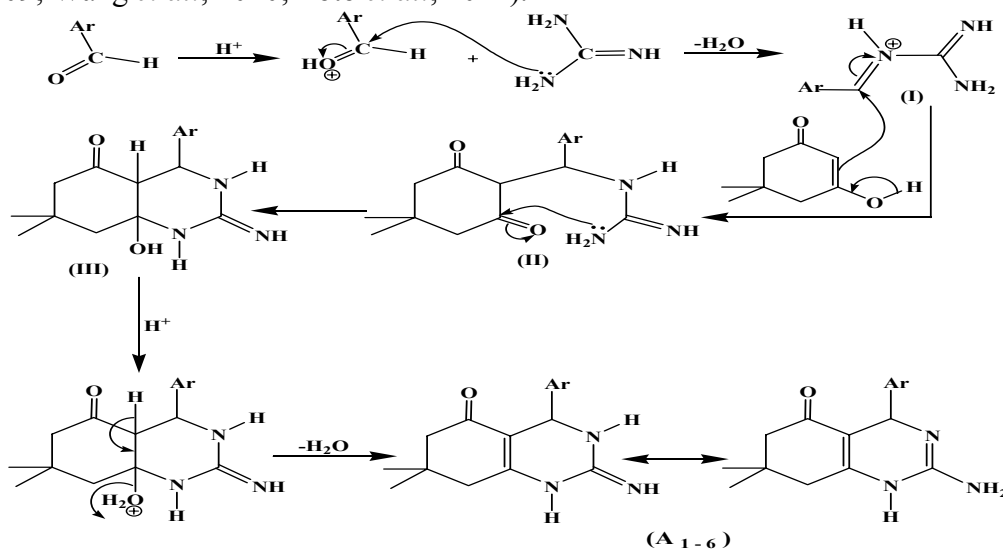
RESULTS AND DISCUSSION

In order to optimize the reaction conditions, we firstly used triethyl amine as a base to prepare compounds (A_{1-6}) and then repeated this reaction under acidic condition according to Biginelli reaction condition by using boric acid (20% mole). This change in reaction condition from basic to acidic proved that the two methods give the same products (A_{1-6}) as shown in equation (1).



Definitely, the acidic condition gave a higher yield than the basic condition, therefore the acidic conditions were adopted to prepare the required compounds (A_{1-6}) (Meshram *et al.*, 2012; Tu *et al.*, 2003). Furthermore, the reaction mechanism in basic conditions is completely different from that in acidic conditions. The reaction mechanism in basic conditions proceed through an ordinary nucleophilic attack of dimedone anion to the carbonyl carbon to afford α,β -unsaturated compound (2-benzylidene-5,5-dimethylcyclohexane-1,3-dione) which then in turn underwent nucleophilic addition reaction with guanidinium hydrochloride to obtained 1-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)(aryl) methyl) guanidine. Finally, intramolecular cycloaddition reaction will occur followed by losing of water molecule to form compound (A_{1-6}), (Singh, 2011).

Whereas, in acidic condition, mechanistically, it is reasonable to assume that the reaction was proceeded firstly via protonation of the carbonyl group then it will undergo nucleophilic attack with guanidinium hydrochloride to afford the intermediate (I) which upon reaction with the enolated form of dimedone yielded the intermediate (II). Finally, intramolecular cycloaddition reaction takes place by the action of amino group on the carbonyl group to give the intermediate (III) followed by losing of water molecule to yield the corresponding compounds (A_{1-6}) as shown in scheme (1), (Hügel, 2009; Wang *et al.*, 2010; Loto *et al.*, 2012).

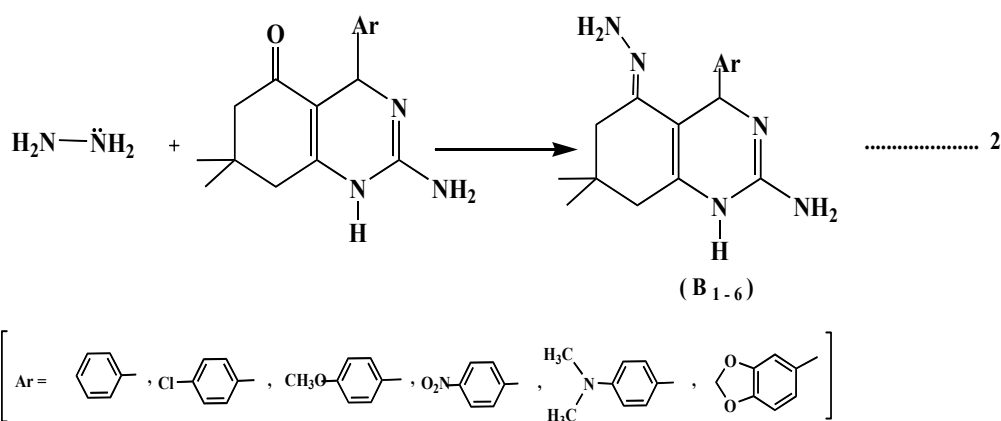


Scheme (1)

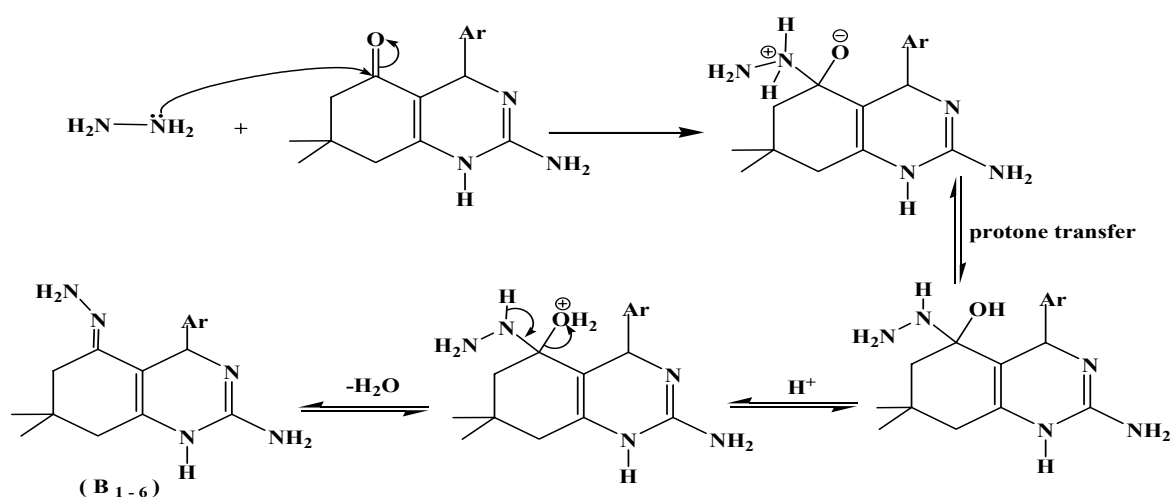
The structures of compounds (A_{1-6}) were confirmed by spectral methods represented by FT-IR and U.V. spectra as shown in Table (1).

In FT-IR spectra all compounds show absorption bands at ($3309-3338\text{ cm}^{-1}$), ($3112-3240\text{ cm}^{-1}$), ($1651-1670\text{ cm}^{-1}$), ($1595-1624\text{ cm}^{-1}$) and ($1547-1612\text{ cm}^{-1}$) due to NH_2 , NH , C=O , C=C (cyclic) and C=N (cyclic) functional groups respectively. Whereas, the U.V. spectra showed absorption bands at λ_{max} ($236-296\text{ nm}$) due to the cyclic system and to the $n \rightarrow \pi^*$ transition (Finar, 1977; Parikh, 1974).

Actually, our target in this work is not only to prepare new Biginelli products but to prove the ability of Biginelli products to act as a good synthon in organic synthesis. Thus, starting from this point and because the Biginelli products (A_{1-6}) having a carbonyl group in position 5, the latter used as good synthon to prepare hydrazones represented by compounds (B_{1-6}) by the action of hydrazine hydrate (80%) in presence of glacial acetic acid and sodium acetate. It is worth noting that, the use of acetic acid and sodium acetate together in this reaction is to keep the reaction under acidic medium (PH 3.7-5.6) (Dawson *et al.*, 1986). The condensation reaction was found to proceed according to equation (2).



The more plausible mechanism for this reaction was summarized in scheme (2). (Schmid, 1996; Clayden *et al.*, 2001).



Scheme (2)

The structures of compounds (B_{1-6}) were established on the bases of their spectral data. Their IR spectra display appearance of absorption bands at ($3263-3373\text{ cm}^{-1}$), ($3124-3224\text{ cm}^{-1}$),

(1604-1620 cm^{-1}), (1508-1562 cm^{-1}) and (1454-1514 cm^{-1}) related to NH_2 , NH , $\text{C}=\text{C}$ (cyclic), $\text{C}=\text{N}$ (imino) and $\text{C}=\text{N}$ (cyclic) functional groups respectively. The absence of keto absorption group at (1651-1670 cm^{-1}) and the appearance of a strong absorption band in the range of (1508-1562 cm^{-1}) attributable to $\text{C}=\text{N}$ (imino) provides an evidence for the formation of schiff bases (B_{1-6}). Also, these compounds have U.V. absorption band at λ_{max} (234-254 nm) due to the $n \rightarrow \pi^*$ transition comparing with those for compounds (A_{1-6}) (Finar, 1977; Parikh, 1974).

Finally, ethyl acetate: benzene, (2:8) was used as a suitable solvent system in R_f thin layer chromatography measurements (Singh, 2011) to provide a suitable explanation about the formation of compounds (A_{1-6}) and (B_{1-6}) as shown in Tables (1) and (2) respectively.

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