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Synthesis of Some Heterocyclic Derivatives of 2-[(2,6-dichloroanilino)Phenyl] Acetic Acid

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Abstract **- 2-[(2,6-dichloroanilino) phenyl] acetic acid) (1) was used as precursor to synthesize new heterocyclic containing derivatives of the carboxylic acid moiety, such as 1,3,4-triazols (8,9,12,13), 1,3,4-thiadiazoles (10,11) and 1,3,4-oxadiazol (14) *via* its reaction with isothiocyanate compounds, followed with a miscellaneous of reagents. The cabohydrazide (3) was incorporated in to 1,3,4-oxadiazol (4), phthalimido derivative (15), tetrazine compound (17), pyrazolines (18-22) and isocyanate compound (24). All the synthesized compounds were characterized by physical and spectral data.**

Keywords- **1,3,4 oxadiazole, 1,3,4 thiadiazole, 1,3,4triazole, tetrazine, thiosemicarbazide.**

I. INTRODUCTION

Diclofenac (2-[(2,6-dichloroanilino)phenyl]acetic acid is well known as one of non-steroidal anti-inflammatory drugs (NSAIDs). (NSAIDs) are well known drugs and considered one of the most widely used therapeutics primarily for treatment of fever, pain and inflammation, especially arthritis [1]. Chronic use of NSAIDs, including diclofenac, may cause appreciable gastrointestinal irritation, bleeding and ulceration [2]. The synthetic approaches based upon NSAIDs chemical modifications by replacement of carboxylic group with heterocyclic moieties have been taken with the aim of improving the efficacy and reducing the ulcerogenicity. It is found that the derivation of the carboxylic function of NSAIDs especially with heterocyclic moiety resulted in an increase in anti-inflammatory activity with reduction in ulcerogenic effect [3,4]. Therefore the search for newer NSAIDs and importance of the heterocyclic moiety as anti-inflammatory agents prompt us to synthesize a new heterocyclic containing Diclofenac derivatives.

II. EXPERIMENTAL SETUP

Melting points were determined with an open capillary tube by electro-thermal melting point apparatus 9300, and were uncorrected. Infrared spectra were recorded as KBr disc on FT.IR-Tensor 27- Bruker Co. Germany, 2003. ^{1}HNMR spectra were recorded on Bruker 400 MHz spectrometer, using TMS as internal standard and (DMSO-d_6) as a solvent.

Synthesis of 2-[2-(2,6-dichloroanilino)phenyl]acetic acid (1)[5]:

Hydrochloric acid solution (10%) was drop wise added to an ethanolic solution of diclofenac sodium salt with stirring until the precipitation completed. The precipitate was filtered off, washed thoroughly with water until the output washing water became neutral, dried and recrystallized from ethanol to give 95% yield of yellowish white material (its m.p. is 155-157 ˚C).

Synthesis of ethyl 2-[2-(2,6-dichloroanilino)phenyl] acetate (2) [6]:

This ester was synthesized by one the following methods:

Method 1:

Concentrated sulfuric acid (5 ml) was added to a clear solution of the substituted acetic acid (1) (0.1 mol) in ethanol. The mixture was refluxed for 20hr then filtered immediately. The resulted solution was concentrated, cooled and finally added to crushed ice. The resulted precipitate was filtered off, washed with water, with a

sodium bicarbonate solution (10%) and with water, dried then recrystallized from ethanol to give 80% yield of white product (its m.p. is 70-72 ^{o}C).

Method 2:

To a clear solution of the acid (1) in ethanol, a concentrated sulfuric acid (20 ml) was gradually added with stirring. The temperature of the resulted solution was raised. The solution was left to cool and then added to a crushed ice. The precipitate was filtered off, washed with sodium carbonate (20%), then thoroughly with water, dried then recrystallized from ethanol to give 95% yield of a white material (its m.p. is 70-72 ^{o}C).

Synthesis of 2-[2-(2,6-dichloroanilino)phenyl]aceto hydrzide (3)[6]:

A mixture of (0.01 mol) of the ester (2) in absolute ethanol (50 ml) and hydrazine hydrate (85%) (0.05 mol) was refluxed for (24 hr). Upon cooling of the reaction mixture, white needle like crystals were separated, filtered off, dried and recrystallized from ethanol to give 80% yield of the hydrazide (3) (its m.p. is 166-168 ^{o}C).

Synthesis of 5-(p-bromophenyl)-2-[(2,6-dichloroanilino) benzyl]-1,3,4-oxadiazole (4)[7,8]:

A mixture of the hydrazide (3) (0.001 mol, 0.31 g) and p-bromobenzoic acid (0.001 mol, 0.21 g) and phosphorous oxychloride (5 ml) was refluxed for (5 hr), cooled then added to a crushed ice. The precipitate was filtered off, washed thoroughly with water, dried then recrystallized from ethanol to give 85% yield of white material (its m.p. is 226-229 ^{o}C).

Synthesis of 1-[{2-(2,6-dichloroanilino)phenyl}acetyl]-4-substituted thiosemicarbazide (5-7)[8,9]:

A mixture of the hydrazide (3) (0.01 mol., 3.1 g) and isothiocyanate compound (0.01 mol) in absolute ethanol (25 ml) was refluxed until the precipitation was completed (2 hr). The mixture was immediately filtrated. The white precipitate was washed with boiled ethanol, dried then recrystallized from absolute ethanol. The physical and spectral data were listed in table I.

Synthesis of 1-amino-2-(aniline/cyclohexylamino)-5-[2-(2,6-dichloroanilino)benzyl]-1,3,4-traiazol (8,9)[8,9]:

A mixture of thiosemicarbazide (5 or 6) (0.001 mol) and hydrazine hydrate (5 ml) was heated for 15 hr at 60 ^{o}C then cooled. The precipitate was immediately formed for compound (5), while in case of compound (6), the mixture must be added to a crushed ice to form the precipitate. The white precipitate was washed thoroughly with water then recrystallized from ethanol. The physical and spectral data were listed Table II.

Synthesis of 2-(anilino/cyclohexylamino)-5-[2-(2,6-dichloroanilino)benzyl)]-1,3,4-thiadiazole (10,11)[8,9]:

To an ice cooled concentrated sulfuric acid (10 ml), the thiosemicarbazide compound (5 or 6) (0.001 mol) was added slowly with stirring within 15 min. The stirring was continued for further 5 hr in an ice bath. The mixture was poured, with stirring, on a crushed ice. The resulted precipitate was filtered off, washed thoroughly with water until the output water became neutral. The solid material was re-dissolved in cold absolute ethanol then filtered. The filtrate was added to a crushed ice. The resulted white precipitate was filtered off, dried and recrystallized from ethanol. The physical and IR spectral data were listed in table III.

Synthesis of 3-[2-(2,6-dichloro anilino)benzyl]-4-(anilino/ cyclohexylamino)-1,2,4-traizolin-5-thione (12,13)[8,9]:

A mixture of compound (5 or 6) (0.001 mol) in 4% sodium hydroxide solution (25 ml) was refluxed for (4 hr) then cooled, filtered and the filtrate was added to a crushed ice. The precipitate was filtered off, washed thoroughly with water, until the output water became neutral, dried then dissolved in cold absolute ethanol. The mixture was filtered, and the filtrate added to a crushed ice. The precipitate was filtered off, dried and recrystallized from ethanol. The physical and IR spectral data were listed in table IV.

Synthesis of 2-anilino-5-[2-(2,6-dichloroanilino)benzyl]-2,3-dihydro-1,3,4-oxadaiazole (14)[10]:

To a solution compound (5) (0.001 mol, 0.044 g) in methanol (25 ml), mercuric oxide (0.001 mol, 0.022 g) was added. The mixture was refluxed for (4 hr) then immediately filtered. The filtrate was concentrated then added to a crushed ice. The precipitate was filtered off, washed with water then dried. The product was redissolved in absolute ethanol, and the mixture was filtered to remove the starting materials. The filtrate was added to a crushed ice to reprecipitate the product. The white solid material was filtered off, dried and recrystallized from ethanol to give 85% yield of m.p.190-192^{o}C.

Synthesis of N-[α-{2-(2,6-dichloroanilino)phenyl} acetamido]phthalimide (15)[11]:

A mixture of the hydrazide (3) (0.001 mol, 0.31 g) and phthalic anhydride (0.001 mol, 0.14 g) in absolute ethanol (25 ml) was refluxed for 15hr. The mixture was filtered before cooling and the filtrate was concentrated, cooled and added, with stirring, to a crushed ice. The resulted precipitate was filtered off, dried then recrystallized from ethanol-water to give 80% yield of white material (its m.p. is 256-257 ^{o}C).

Synthesis of N'-benzoyl-α-[2-(2,6-dichloroanilino)phenyl] acethydrazide (16)[12]:

To solution of the hydrazide (3) (0.001 mol, 0.31 g) in dry benzene (20 ml), benzoyl chloride (0.001 mol, 0.14 g) was drop wise added with stirring. The stirring was continued until the solution becomes clear. The mixture was refluxed for (~2 hr) to complete the precipitation. The mixture was filtered, before cooling, and the precipitate was washed with hot dry benzene, to remove the starting materials, dried and recrystallized from ethanol to give a white solid material (its m.p. is 234-236 ^{o}C).

Synthesis of 1,2-dihydro-3-phenyl-6-[2-(2,6-dichloro anilino)benzyl]-1,2,4,5-tetrazine (17)[12]:

A mixture of compound (16) (0.005 mol, 2 g) and hydrazine hydrate (10 ml) in absolute ethanol (20 ml) was refluxed for (15 hr). The mixture was concentrated, cooled then added with stirring to a crushed ice. The precipitate was filtered off, dried then recrystallized from n-heptane to give white solid material (its m.p. is 153-54 ^{o}C).

Synthesis of 5-phenyl-3-(aryl/alkyl)-2-[α-{2-(2,6-dichloro anilino)phenyl}acetyl]-3,4-dihydro-1H-pyrazole (18-22) [13]:

To solution of the hydrazide (3) (0.005 mol,1.55 g) in ethanol (25 ml), an alcoholic sodium hydroxide solution (45%, 5 ml) was added with stirring. The mixture was heated to 40 ^{o}C and one of the chalcones (0.005 mol) was added with stirring. The stirring was continued for further (2 hr) then concentrated under reduced pressure. The resulted residue was washed thoroughly with water, until the output water became neutral, dried then recrystallized from ethanol-water. The physical and spectral data of compounds (18-22) were listed in table V.

Synthesis of α-[2-(2,6-dichloroanilino)phenyl]acetylazide (23)[14]:

To a suspended solution of the azide (3) (0.005 mol, 1.55 g) in water (10 ml) and concentrated hydrochloride acid (4 ml), a solution of sodium nitrite (0.025 mol, 1.7 g) in water (10 ml) was drop wise added with stirring under cooling at (-5 ^{o}C). The mixture was stirred for further (6 hr) at the same temperature. The yellow residue was filtered off, washed thoroughly with water then dried (its m.p. is 58-60 ^{o}C).

Synthesis of 2-(2,6-dichloroanilino)benzylisocyanate (24) [15]:

A solution of compound (23) (0.01 mol, 3.21 g) in dry toluene (10 ml) was refluxed for (15 min) and the resulted precipitate was filtered off, washed with hot toluene, dried and recrystallized from benzene to give 85% yield of white solid product (its m.p.is 222-224 ^{o}C).

Reaction of isocyanate compound (24) with miscellaneous compounds [14]:

A mixture of isocyanate compound (24) (0.01 mol, 2.9 g) and different compounds (such as aniline, substituted aniline, alcohols, phenols, and hydrazines) (0.01 mol) in DMF (25 ml) was refluxed for different times, then

filtered immediately. The filtrate was cooled then poured on a crushed ice. The resulted precipitate was filtered off, washed with water, dried then recrystallized from ethanol to give brown product. Interestingly, all the reactions gave a same product (its m.p. is 120-122 ^{o}C), which is identified as 1-(2,6-dichlorophenyl)-3,4-dihydro quinazoline-2(H)-one. On the other hand, refluxing of compound (24) in DMF onlyb gave, also, the same product.

III. RESULTS AND DISSCUSION

The process for synthesis of heterocyclic compounds is out lined in Scheme 1.

The key intermediate for preparation of variety of heterocyclic compounds is the carbohydrazide derivative (3) of 2-[2-(2,6-dichloroanilino)phenyl]acetic acid (1). This hydrazide is readily synthesized via conventional esterification of the acid (1) *via* its reaction with ethanol in presence of sulfuric acid, followed by treatment of the resulted ester (2) with excess of hydrazine hydrate in absolute ethanol. The IR spectrum of the ester (2) showed absorption bands for C=O bond stretching at 1732 cm^{-1}, N-H bond stretching at 3249 cm^{-1} and C-Cl bond stretching at 798 cm^{-1} in addition to two bands at 1105 and 1173 cm^{-1} for symmetrical and asymmetrical C-O-C bonds stretching respectively. The IR spectrum of the hydrazide (3) revealed the appearance of stretching bands for N-H bond at 3329 cm^{-1} and the band for C=O bond stretching was shifted to lower frequency at 1635 cm^{-1} compared with that of ester due to tautomersim. The observed peaks in ^{1}HNMR spectrum were identical with the chemical structure of the hydrazide (3), whereas it appeared five peaks: δ(ppm): 3.52 (s, 2H, CH_2); 4,33 (S, 2H, NH_2); 6.32 (s, 1H, NH), 6.33-8.42 (m, 7H, Ar-H), 9.49 (S,1H, CONH) [17, 18].

The hydrazide (3) was reacted with p-bromobenzoic acid in presence of $POCl_3$ as a chlorinating, cyclization and dehydrating agent to form 1,3,4-oxadiazole compound (4). The IR spectrum of this compound exposed the appearance of a stretching band for C=N endocyclic bonds at 1680 cm^{-1} and two bands at 1068 &1279 cm^{-1} for C-O-C symmetrical and asymmetrical bonds stretching respectively.

On the other hand, the reaction of the hydrazide (3) with isothiocyanate compounds, namely, phenyl, cyclohexyl and allyl isothiocyanate yielded the thiosemecarbazides (5-7). The IR spectra of these compounds showed absorption bands at 1670-1668 cm^{-1} for C=O bond stretching and at 1146-1205 cm^{-1} for C=S bond stretching. The compounds (5&6) were used as precursors to synthesize the heterocyclic derivatives (8-14) via their reaction with various reagents. The reaction of compounds (5&6) with hydrazine hydrate afforded 1-aminotriazoles (8&9). The IR spectra of these compounds showed absorption bands at 1624-1635 cm^{-1} for C=N bond stretching. It was, also, exposed the absence of stretching bands of C=O and C=S bonds. ^{1}HNMR spectrum of compound (8) showed chemical shifts δ(ppm) at: 3.35 (s, 2H, CH_2), 3.93 (S, 2H, NH_2), 6.16 (S, 1H, NH) and 6.77-7.54 (m, 12H, Ar-H).

moreover, refluxing of compounds (5&6) in acidic medium afforded 1,3,4-thiadiazoles (10&11) via thermal intra molecular cyclization process. The IR spectra of compounds (10&11) exposed the absence of stretching bands of C=O and C=S groups and appearance of absorption bands at 1562 and 1604 cm^{-1} related to C=N bond stretching. The ^{1}HNMR spectrum of compound (10) showed a characteristic chemical shifts δ(ppm) at: 4.41 (S, 2H, CH_2), 6.18 (S, 1H, NH), 6.85-7.57 (m, 12H, Ar-H), 10.44 (S, 1H, het-NH).

Furthermore, the compounds (5&6) were subjected to a cyclization reaction by refluxing with aqueous sodium hydroxide solution (4%) to give 1,2,4-triazole-5-thiol compounds (12&13). The structure of these compounds were resonated between the thione and thiol forms. The IR spectra of compounds (12&13) exposed the absence of stretching bands of C=O bond and appearance of C=N bond stretching bands at 1592 and 1647 cm^{-1} and C=S bond stretching band at 1169 and 1190 cm^{-1}. The ^{1}HNMR for compound (12) was more informative, characteristic chemical shifts were observed δ(ppm) at: 3.94 (S, 2H, CH_2), 6.18 (S, 1H, NH), 6.72-7.52 (m, 12H, Ar-H) and 13.78 (S, 1H, SH).

Moreover treatment of compound (5) with mercuric oxide in methanol afforded 1,3,4-oxadiazol compound

(14). The IR spectrum indicated the absence of C=O and C=S bond stretching bands and appearance of C=N bond stretching band at 1603 cm^{-1} and two bands at 1032-1232 cm^{-1} for symmetrical and asymmetrical C-O-C bonds stretching.

On the other hand, the hydrazide (3) can, also, be used to synthesize another new compounds. Interesting, was allowed to react with phthalic anhydride to produce a phthalimide derivative (15). Its IR spectrum showed absorption bands at 1680 and 1652 for the phthalimide and amid C=O bond stretching respectively. ^{1}HNMR spectrum showed a characteristic chemical shifts δ(ppm) at: 3.85 (S, 2H, CH_2), 6.32 (S,1H, NH) and 6.95-7.98 (m,12H, Ar-H, NHCO).

Moreover, the hydrazide (3) was, also, treated with benzoyl chloride to from the diacyl hydrazine compound (16), which was, then, converted to the tetrazine (17), by its refluxing with hydrazine hydrate in ethanol. The IR spectrum of compound (16) showed absorption bands at 1668 and 1630 cm^{-1} for the two C=O bonds stretching, while the IR spectrum for tetrazine compound (17) showed absorption band at 1656 cm^{-1} for the C=N bond stretching and absence of C=O bond stretching.

The synthesis of a series of pyrazoline compounds (18-22) was carried out via treatment of the hydrazide (3) with alcoholic sodium hydroxide solution (45%), then with one of the synthesized chalcones via Michel addition [13]. The IR spectra of compounds (18-22) revealed the appearance of stretching bands for N-H and C=O bonds at 3282-3232 and 1664-1643 cm^{-1} respectively. The ^{1}HNMR spectrum of compound (22) showed a characteristic chemical shifts δ(ppm) at: 3.31(d, 2H, cyclic CH_2), 4.01 (t, 1H, cyclic CH), 4.23 (S, 2H, CH_2), 6.27 (S, 1H, NH), 6.8-7.86 (m, 16H, Ar-H).

The hydrazide (3) was, also, converted to the azide derivative (23) via its reaction with nitrous acid under cooling. The azide gave a characteristic absorption band in IR spectrum for the azide (N_3) bond stretching at 2140 cm^{-1}, in addition to C=O bond stretching at 1720 cm^{-1}. This azide underwent Curtis rearrangement under boiling in dry toluene to give an isocyanate compound (24). The IR spectrum of this compound showed a characteristic absorption band at 2266 cm^{-1} related to the (N=C=O) bonds stretching. The ^{1}HNMR showed three chemical shifts δ(ppm) at: 4.32 (s, 2H, CH_2), 6.31 (s, 1H, NH), 6.78-7.5 (m, 7H,Ar-H).

Finally, the reaction of the isocyanate compound (24) with various amines, alcohols and phenols does not afforded the expected products (substituted urea and carbamate derivatives respectively), but all reactions afforded same product which is 1-(2,6-dichlorophenyl)-3,4-dihydro quinazoline-2(1H)-one (25). This means that the intra-molecular cyclization reaction the isocyanate compound occurred before the intermolecular reaction between the isocyanate compound and the previous mentioned compounds. The IR spectrum of compound indicated the absence of N=C=O bond stretching at 2266 Cm^{-1} and appearance of C=O and C=C bond stretching bands at 1690 and 1610 Cm^{-1}.

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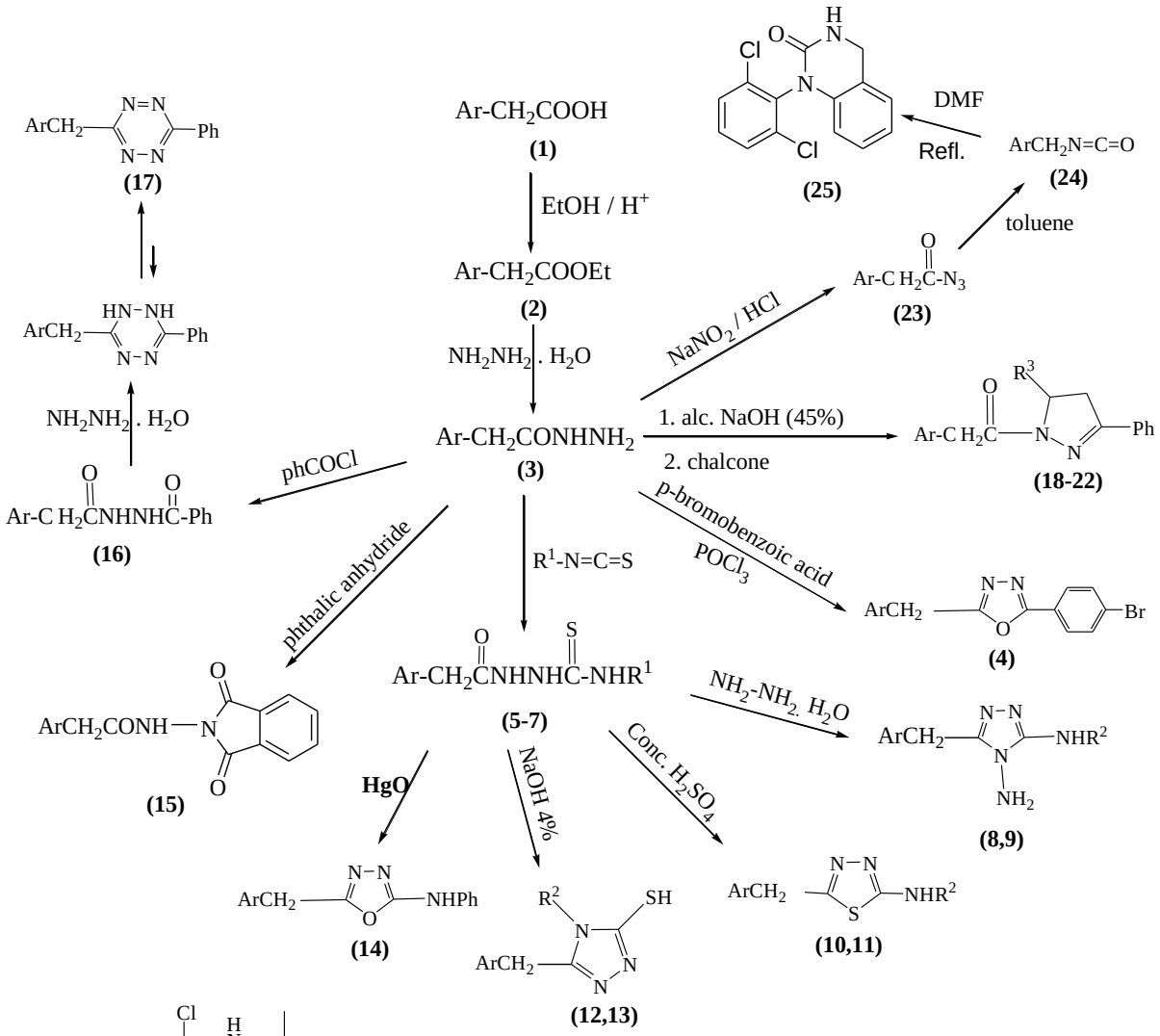

Scheme 1

Table I

Physical and spectral data of compounds (5-7)

Compd. No.	R_1	M.P. (°C)	Yield (%)	IR ν (Cm^{-1})			
				N-H	C=O	C=C	C=S
5	phenyl	166-167	92	3221	1670	1589	1163
6	Cyclohexyl	200-201	90	3276	1668	1533	1146
7	Allyl	207-208	88	3182	1684	1545	1202

Table II

Physical and spectral data of compounds (8,9)

Compd. No.	R_1	M.P. (°C)	Yield (%)	IR ν (Cm^{-1})		
				N-H	C=C	C=N
8	Ph-	248-250	87	3300	1576	1624
9	C_6H_{11}-	140-143	77	3327	1587	1635

Table III

Physical and IR spectral data of compounds (10,11)

Compd. No.	R	M.P. (°C)	Yield (%)	IR ν (Cm^{-1})	
				C=N	N-H
10	ph-	302-304	77	1562	3180
11	C_6H_{11}-	163-165	79	1604	3259

Table IV

Physical and spectral data of compounds(12,13)

Compd. No.	R_1	M. P. (°C)	Yield (%)	Color	IR ν (cm^{-1})		
					N-H	C=N	C=S
12	Ph-	268-270	70	Faint brown	3259	1604	1196
13	C_6H_{11}-	212-214	73	white	3180	1562	1190

Table V

Physical and spectral data of compounds (18-22).

Compd. No.	R	M. P. (°C)	Yield (%)	Color	IR ν (cm^{-1})	
					N-H	C=O
18	2-Cl-ph	210-212	65	white	3240	1654
19	styryl	94-96	60	Yellowish-white	3282	1655
20	ph	99-102	56	Orange	3279	1664
21		170-173	55	Yellowish-orange	3232	1664
22	4-Cl-ph	214-216	62	white	3267	1643