

## Synthesis of Barbiturate Derivatives from Imines

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### Abstract

Barbiturates were prepared involving the reaction of aromatic Schiff bases with benzoyl chloride to give N-[ $\alpha$ -chloro- $\alpha$ -dimethylaminobenzyl]-N-aryl-benzanilide. The reaction of the latter with diethylmalonate in basic media to give N-[ $\alpha$ -diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilide. The latter condense with urea in basic media afforded derivatives of barbiturate which known to act as hypnotics.

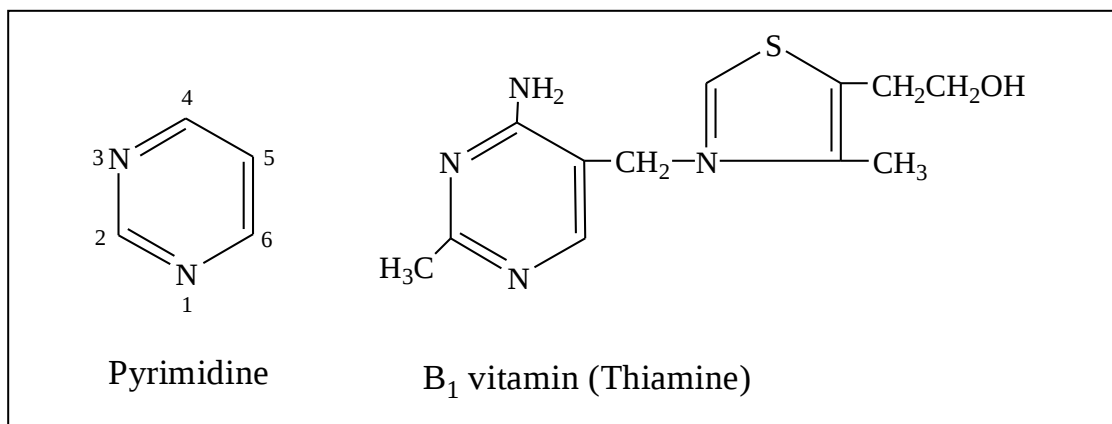
### Introduction

In recent years there has been an increased interest in the chemistry of heterocyclic molecules because of their biological significance<sup>(1)</sup>. Schiff bases can be used in industrial chemistry and inorganic chemistry field<sup>(2,3)</sup>. There are many methods found in the literatures to prepare Schiff bases, specially through the condensation of aldehydes or ketenes with primary amines<sup>(4)</sup>. Also reduction of nitriles compounds were carried out either by lithium Aluminum Hydride (LiAlH<sub>4</sub>) or addition of Grignard reagent afforded the imines<sup>(5,6)</sup>.

In this paper we reported a new method to synthesis of barbiturate derivatives from the aromatic Schiff bases.

Barbiturates are compounds contain a pyrimidine ring<sup>(7)</sup>. Pyrimidine is a six-membered ring with two nitrogen atoms. The chemistry of pyrimidine compounds and its biochemistry are very important especially in the biosynthesis of lipids derivatives and complex carbohydrates<sup>(8)</sup>. Pyrimidines are constituent of an important products like drags that are used as anti bacterial and malaria<sup>(9)</sup>, B<sub>1</sub> and B<sub>2</sub> vitamins<sup>(9)</sup>, coffee

and tea in their caffeine's<sup>(10)</sup>. Medically the barbiturates which are important pyramiding derivatives are used as hypnotics<sup>(11)</sup>.



## Experimental

Melting points (M.P.) were measured by: Stuart Melting point Apparatus and were uncorrected. Infrared spectra (FT.IR) were recorded as (KBr) discs by: Shimadzu 8400 FTIR Spectrophotometer in the range (4000-450)  $\text{cm}^{-1}$ . Ultra violet-visible spectra were recorded in the region (900-200) nm for  $10^{-3}$  m solution in (EtOH) at  $25^\circ\text{C}$  by: Shimadzu 160 spectrophotometer.

## Synthesis of Schiff bases<sup>(12)</sup>

A mixture of equimolar amounts (0.015mole) of aromatic aldehydes and primary amine was dissolved in (20ml) of absolute ethanol containing a drop of glacial acetic acid and refluxed for (2hrs). the reaction mixture was allowed to cool to room temperature then filtered. Re-crystallization from ethanol gave a colored crystals of: N-benzylideneareneamines [1-4].

## Synthesis of N- $\alpha$ -chlorobenzyl-N-aryl-benzailide<sup>(13)</sup>

Acetyl chloride solution (0.01mole) in (10ml) absolute benzene was added dropwise to the solution (0.01mole) benzylideneareneamine dissolved in (25ml) absolute benzene. The reaction mixture was refluxed for (2hrs.) with stirring. The solution was normally allowed to cool at room temperature, and the precipitated crystals were filtered and re-crystallized from ethanol to yield colored crystals of: N- $\alpha$ -chlorobenzyl-N-aryl-benzailides[5-8].

## Synthesis of N-[ $\alpha$ -diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilide

A mixture of (0.01mole) of diethyl malonate and (10ml) of ethanolic solution of sodium ethoxide was added to a solution of (0.01mole) of N-[ $\alpha$ -chloro- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilide in (20ml) of absolute ethanol. The reaction

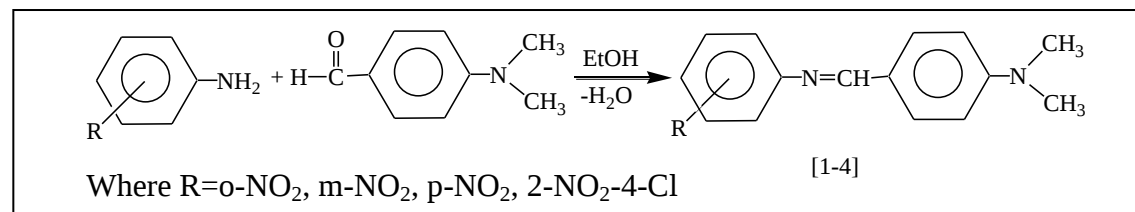
mixture was refluxed for (4hrs.) with stirring. The solvent was evaporated. The resulting was allowed to cool to room temperature, and the participated crystals was filtered, washed with 2% Na<sub>2</sub>CO<sub>3</sub> solution, then re-crystallized from ethanol to give: N-[ $\alpha$ -diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilide[9-12].

#### Synthesis of $\alpha$ -[N-benzyl-N-aryl]amino- $\alpha$ -p-dimethylaminobenzyl-barbituric acid

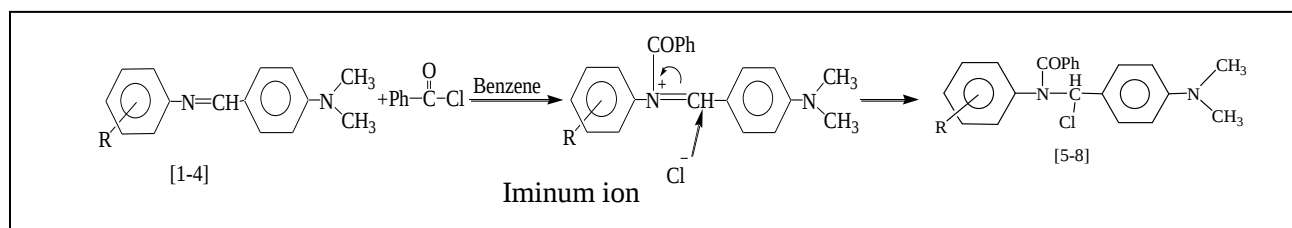
A solution of (0.005mole) of urea in (15mL) of dry acetone was added to a solution of (0.005mole) of N-[ $\alpha$ -diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilide in (15mL) of dry acetone. The reaction mixture was refluxed for (7hrs.) with stirring. The solvent was evaporated and the remaining crystals was filtered, re-crystallized from ethanol to yield:  $\alpha$ -[N-benzyl-N-aryl]amina- $\alpha$ -p-dimethylaminobenzyl-barbituric acids[13-16].

#### Result and Discution

Aromatic Schiff bases are good starting material to prepare heterocyclic compounds<sup>(12)</sup>. Aromatic Schiff bases were prepared by acid-catalyzed reaction of aromatic aldehydes with aromatic amines in boiling absolute ethanol<sup>(12)</sup>.



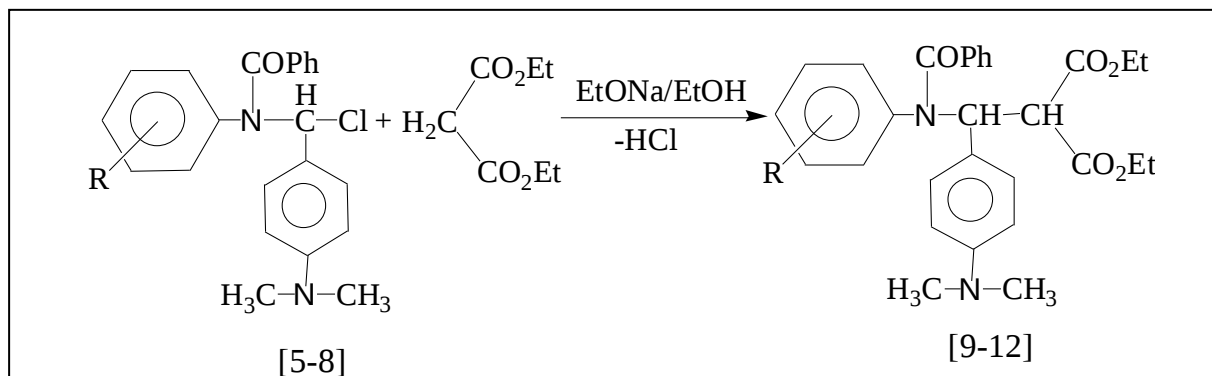
Schiff bases are react with benzoyl chloride to yield N- $\alpha$ -chlorobenzyl-benzanilide [5-8] in good yield<sup>(13)</sup>.



The nitrogen atom attacks the carbon atom of the carbonyl group displacing the chloride ion to form iminium ion. Chloride ion attacks the iminium carbon yields benzanilide derivatives [5-8]. The IR spectra of compounds [5-8] showed an absorption band at (1640-1665)cm<sup>-1</sup> due to (C=O) of  $\left( \begin{smallmatrix} \text{O} \\ \parallel \\ \text{N}-\text{C} \end{smallmatrix} \right)$  group, appearance of aliphatic (C-Cl) absorption band at (825-830)cm<sup>-1</sup>(14).

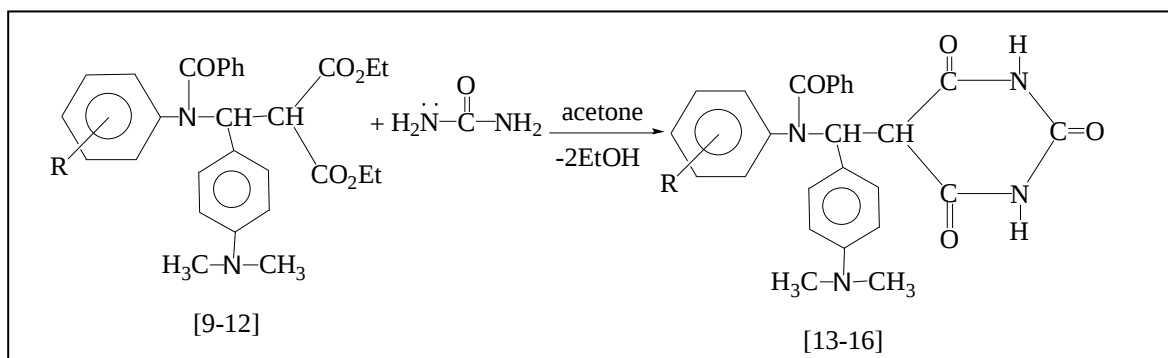
The U.V spectra of compounds [5-8] showed absorption maxima at (305-343)nm due to charge transferee.

N-[ $\alpha$ -chloro- $\alpha$ -dimethylaminobenzyl]-N-aryl-benzanilides undergo nucleophilic substitution reaction when treated with diethyl malonate in basic medium to give N-[ $\alpha$ -P-diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilides [9-12] with elimination of HCl.



The IR of compounds [9-12] gave an absorption band about  $(1755-1735)\text{cm}^{-1}$  due to C=O of ester, and around  $(1685-1670)\text{cm}^{-1}$  due to C=O of amide, and disappearance of aliphatic (C-Cl) band at  $(830-825)\text{cm}^{-1}$ .<sup>(14)</sup>

The U.V spectra showed absorption maxima at  $(358-219)\text{nm}$ . N-[ $\alpha$ -diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilides [9-12] are condensed with urea by nucleophilic substitution to give the pyrimidine derivatives (barbiturates) [13-16].



The IR for barbiturate derivatives gave an absorption band at  $(3280-3260)\text{cm}^{-1}$  due to (N-H), and at  $(1690-1680)\text{cm}^{-1}$  due to  $\left(\text{—NH—C}(=\text{O})\right)$ .<sup>(14)</sup>

The U.V spectra of barbiturate derivatives showed absorption maxima at  $(380-210)\text{nm}$ .

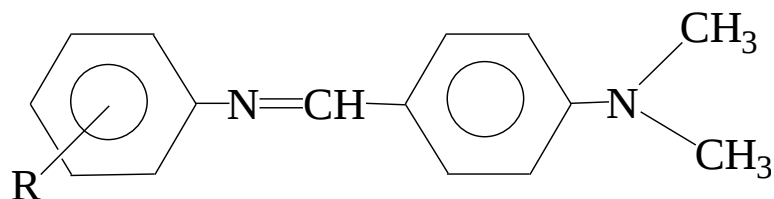


Table (I): Physical and spectroscopic data of imines[1-4]

| Comp. | R                       | Molecular formula                                                | m.p.C°  | Yield % | F.T.I.R. $Cm^{-1}$ (KBr) |                          |                          |             |                |              | U.V.<br>$\lambda_{max}nm$<br>(EtOH) |
|-------|-------------------------|------------------------------------------------------------------|---------|---------|--------------------------|--------------------------|--------------------------|-------------|----------------|--------------|-------------------------------------|
|       |                         |                                                                  |         |         | $\nu_{C=N}$              | $\nu_{C=H}$<br>aliphatic | $\nu_{C=H}$<br>aliphatic | $\nu_{C=N}$ | $\nu_{C=NO_2}$ | $\nu_{C=Cl}$ |                                     |
| 1     | o-NO <sub>2</sub>       | C <sub>15</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub>    | 103-105 | 58      | 1603                     | 3050                     | 2845                     | 1245        | 1519&1342      | -            | 243                                 |
| 2     | m-NO <sub>2</sub>       | C <sub>15</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub>    | 148-150 | 61      | 1598                     | 3045                     | 2843                     | 1240        | 1504&1334      | -            | 242                                 |
| 3     | p-NO <sub>2</sub>       | C <sub>15</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub>    | 198-200 | 69      | 1598                     | 3050                     | 2845                     | 1243        | 1504&1373      | -            | 248                                 |
| 4     | 2-NO <sub>2</sub> ,4-Cl | C <sub>15</sub> H <sub>14</sub> O <sub>2</sub> N <sub>3</sub> Cl | 222-224 | 51      | 1604                     | 3055                     | 2850                     | 1245        | 1520&1340      | 817          | 238                                 |

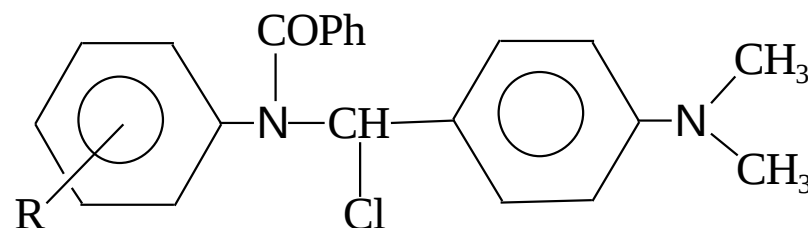


Table (II): Physical and spectroscopic data of N-[ $\alpha$ -chloro- $\alpha$ -dimethylaminobenzyl]-N-aryl-benzanilide.[5-8]

| Comp. | R                       | Molecular formula                                                             | m.p.C°  | Yield % | F.T.I.R. Cm <sup>-1</sup> (KBr) |                                 |                                 |                    |                       |                     | U.V.<br>$\lambda_{\max}$ nm<br>(EtOH) |
|-------|-------------------------|-------------------------------------------------------------------------------|---------|---------|---------------------------------|---------------------------------|---------------------------------|--------------------|-----------------------|---------------------|---------------------------------------|
|       |                         |                                                                               |         |         | $\nu_{\text{C=N}}$              | $\nu_{\text{C=H}}$<br>aliphatic | $\nu_{\text{C=H}}$<br>aliphatic | $\nu_{\text{C=N}}$ | $\nu_{\text{C=NO}_2}$ | $\nu_{\text{C=Cl}}$ |                                       |
| 5     | o-NO <sub>2</sub>       | C <sub>22</sub> H <sub>20</sub> O <sub>3</sub> N <sub>3</sub> Cl              | 171-173 | 62      | 1640                            | 3060                            | 2860                            | 1245               | 1545&1330             | 830                 | 305                                   |
| 6     | m-NO <sub>2</sub>       | C <sub>22</sub> H <sub>20</sub> O <sub>3</sub> N <sub>3</sub> Cl              | 197-199 | 80      | 1660                            | 3050                            | 2850                            | 1240               | 1540&1345             | 825                 | 336                                   |
| 7     | p-NO <sub>2</sub>       | C <sub>22</sub> H <sub>20</sub> O <sub>3</sub> N <sub>3</sub> Cl              | 210-212 | 83      | 1650                            | 3050                            | 2855                            | 1240               | 1540&1343             | 825                 | 305                                   |
| 8     | 2-NO <sub>2</sub> ,4-Cl | C <sub>22</sub> H <sub>19</sub> O <sub>3</sub> N <sub>3</sub> Cl <sub>2</sub> | 257-260 | 65      | 1665                            | 3063                            | 2865                            | 1245               | 1540&1350             | 830                 | 343                                   |

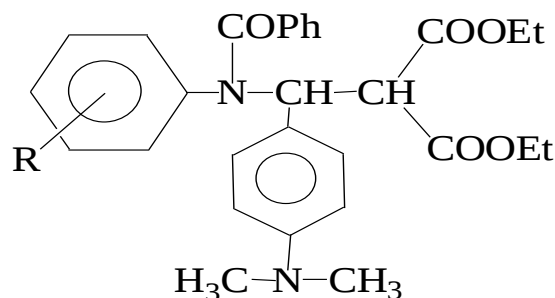


Table (III): Physical and spectroscopic data of N-[ $\alpha$ -diethylmalonyl- $\alpha$ -p-dimethylaminobenzyl]-N-aryl-benzanilide[13-16].

| Comp. | R                       | Molecular formula                                             | m.p.C°  | Yield % | F.T.I.R. Cm <sup>-1</sup> (KBr) |                             |                                 |                                 |                    |                      |                       |                     | U.V.<br>$\lambda_{\max}$ nm<br>(EtOH) |
|-------|-------------------------|---------------------------------------------------------------|---------|---------|---------------------------------|-----------------------------|---------------------------------|---------------------------------|--------------------|----------------------|-----------------------|---------------------|---------------------------------------|
|       |                         |                                                               |         |         | $\nu_{\text{C=O}}$<br>amide     | $\nu_{\text{C=O}}$<br>ester | $\nu_{\text{C-H}}$<br>aliphatic | $\nu_{\text{C-H}}$<br>aliphatic | $\nu_{\text{C=N}}$ | $\nu_{\text{C-O-C}}$ | $\nu_{\text{C=NO}_2}$ | $\nu_{\text{C=Cl}}$ |                                       |
| 9     | o-NO <sub>2</sub>       | C <sub>29</sub> H <sub>31</sub> O <sub>7</sub> N <sub>3</sub> | 225-227 | 57      | 1670                            | 1750                        | 3055                            | 2850                            | 1240               | 1240<br>1130         | 1540&1345             | -                   | 343 238                               |
| 10    | m-NO <sub>2</sub>       | C <sub>29</sub> H <sub>31</sub> O <sub>7</sub> N <sub>3</sub> | 239-241 | 70      | 1670                            | 1745                        | 3045                            | 2850                            | 1240               | 1240<br>1130         | 1535&1340             | -                   | 345 219                               |
| 11    | p-NO <sub>2</sub>       | C <sub>29</sub> H <sub>31</sub> O <sub>7</sub> N <sub>3</sub> | 252-254 | 68      | 1675                            | 1750                        | 3045                            | 2850                            | 1240               | 1240<br>1130         | 1540&1340             | -                   | 358 240                               |
| 12    | 2-NO <sub>2</sub> ,4-Cl | C <sub>29</sub> H <sub>30</sub> ON <sub>3</sub> Cl            | 280-283 | 46      | 1685                            | 1755                        | 3058                            | 2850                            | 1245               | 1245<br>1136         | 1545&1335             | 830                 | 344 239                               |

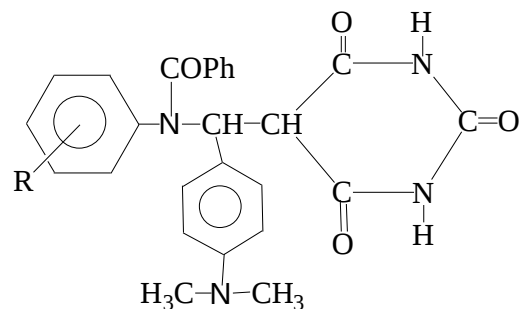


Table (IV): Physical and spectroscopic data of  $\alpha$ -[N-benzyl-N-aryl]amino- $\alpha$ -p-dimethylaminobenzyl-barbituric acid[13-16]

| Comp. | R                       | Molecular formula                                                | m.p.C°  | Yield % | F.T.I.R. $\text{Cm}^{-1}(\text{KBr})$ |                              |                                       |                                 |                                 |                    |                       |                     | U.V.<br>$\lambda_{\text{maxnm}}$<br>(EtOH) |
|-------|-------------------------|------------------------------------------------------------------|---------|---------|---------------------------------------|------------------------------|---------------------------------------|---------------------------------|---------------------------------|--------------------|-----------------------|---------------------|--------------------------------------------|
|       |                         |                                                                  |         |         | $\nu_{\text{N-H}}$                    | $\nu_{\text{C=O}}$<br>lactam | $\nu_{\text{C=O}}$<br>amide $3^\circ$ | $\nu_{\text{C=H}}$<br>aliphatic | $\nu_{\text{C=H}}$<br>aliphatic | $\nu_{\text{C=N}}$ | $\nu_{\text{C=NO}_2}$ | $\nu_{\text{C=Cl}}$ |                                            |
| 13    | o-NO <sub>2</sub>       | C <sub>26</sub> H <sub>23</sub> O <sub>6</sub> N <sub>5</sub>    | 257-259 | 45      | 3275                                  | 1685                         | 1665                                  | 3050                            | 2855                            | 1245               | 1545&1335             | -                   | 344 210                                    |
| 14    | m-NO <sub>2</sub>       | C <sub>26</sub> H <sub>23</sub> O <sub>6</sub> N <sub>5</sub>    | 269-270 | 56      | 3260                                  | 1580                         | 1660                                  | 3045                            | 2850                            | 1240               | 1540&1340             | -                   | 380 245                                    |
| 15    | p-NO <sub>2</sub>       | C <sub>26</sub> H <sub>23</sub> O <sub>6</sub> N <sub>5</sub>    | 279-281 | 49      | 3270                                  | 1685                         | 1670                                  | 3045                            | 2855                            | 1240               | 1540&1340             | -                   | 304 247                                    |
| 16    | 2-NO <sub>2</sub> ,4-Cl | C <sub>26</sub> H <sub>22</sub> O <sub>6</sub> N <sub>5</sub> Cl | 295-298 | 43      | 3280                                  | 1690                         | 1680                                  | 3048                            | 2860                            | 1240               | 1545&1330             | 830                 | 300 247                                    |

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تحضير مشتقات الباربيتورات من الایمینات .

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الخلاصة

تحضر الباربيتورات من تفاعل قواعد شیف الاروماتیة مع كلورید البنزویل لیعطي N - [  $\alpha$  - کلورید -  $\alpha$  - ثنائي مثیل أمینو بنزویل ] - N - آریل - بنزانیلید . تتفاعل الاخيرة مع ثنائي أثیل مالونیت فی وسط قاعدي لتعطي N - [  $\alpha$  - ثنائي أثیل مالونیل -  $\alpha$  - بارا - ثنائي مثیل أمینو بنزویل ] - N - آریل - بنزانیلید . تتکاثف الاخيرة مع یوریا فی وسط قاعدي لتعطي مشتقات الباربيتورات التي تستعمل كـ " منومات " .