SYNTHESIS OF N\textsuperscript{1}-ALKYL AND N\textsuperscript{1}-ALLYL OF PHENYLHYDRAZONES

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Keywords: N-Acetylenzophenylhydrazones, N-alkyldrazones

Abstract

A general and convenient method for preparation of N\textsuperscript{1}-alkyl and N\textsuperscript{1}-allylphenyldrazones is described and their reactivity towards ketene is studied.

Introduction

In continuation of our interest on the reaction on imines with ketenes [1], we needed substantial amounts of N\textsuperscript{1}-substituted phenyldrazones. In preparation of N\textsuperscript{1}-alkyl or N\textsuperscript{1}-allylphenyldrazones, however, we found out that no convenient synthetic method is available. There are spread reports in the literature and in most cases two steps sequence (1 → 2 → 4) (scheme 1) is utilized for the synthesis of N\textsuperscript{1}-substituted phenyldrazones [2,3]. The synthesis of N\textsuperscript{1} alkylphenyldrazones by this method is problematic for several reasons. First, since both hydrazine (1) and (2) are liquid with similar physical properties, separation and purification of N\textsuperscript{1}-alkylphenyldrazine from the reaction mixture is difficult and resulting in low yield. Another problem in the synthesis of (4) by this route is that condensation of N\textsuperscript{1}-allylphenyldrazine (2) with aldehydes and ketones, when comparing with simple non-alkylphenyldrazine is rather difficult. Steric factor caused by substitution at N\textsuperscript{1} position may be responsible for this low reactivity.

Results and Discussion

Alternative method, i.e., 1 → 3 → 4 is, to our knowledge, the simplest route for preparation of compounds (4). In 1990 Sherma et al. reported the preparation of only N-Methylphenyldrazone by this method, claiming quantitative yield [4]. We repeated Sherma procedure several times, but the yields obtained were hardly more than 40 percent. By changing the reaction condition (see experimental section) we were able to alkylate phenyldrazone (3) with various alkyl and allylhalide in good yields (table 1).
In preparation of hydrazone (4a-h), (3a-h) were treated with sodium amide in tetrahydrofuran (THF) to give corresponding anions. When these anions allowed to react in situ with appropriate alkyl halide, N\(^1\)-alkylated hydrazones (4a-h) were formed in good yield and good purity. No by-products were detected and work-up condition were straightforward. THF may be replaced by dimethoxethane as solvent without appreciable loss in yield and purity. However, sodium amide proved to be superior to sodium hydride and n-buthyllithium as deprotonationg agent. Alkyl iodide, bromide or chloride afforded comparable yields.

In pursuing our interest, the next step was to examine the reactivity of hydrazones with ketene. These reactions should be of interest, since they could lead either to \(\beta\)-lactam rings[1] or acetylhydrazones.

Addition of ketene, produced by pyrolysis of acetone at 700-750°C, to phenylhydrazones (3a-e) gave N\(^1\)-acycl phenylhydrazones (6a-e) in high yield (table 2).
Synthesis of N1-Alkyl and N1-Allyl of Phenylhydrazones

Table 2. Preparation of N1-acetylphenylhydrazones (6a-e) from ketone

<table>
<thead>
<tr>
<th>Compound</th>
<th>G</th>
<th>Y</th>
<th>Reaction Time (hr)</th>
<th>Yield%</th>
<th>m.p.(C)</th>
<th>Formula or Lit.m.p.(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>4</td>
<td>95</td>
<td>120-121</td>
<td>122[6]</td>
</tr>
<tr>
<td>b</td>
<td>4-Cl</td>
<td>H</td>
<td>8</td>
<td>91</td>
<td>87-8</td>
<td>Cl5H13CN2O</td>
</tr>
<tr>
<td>c</td>
<td>4-NO2</td>
<td>H</td>
<td>8</td>
<td>90</td>
<td>164-5</td>
<td>Cl5H13NO3</td>
</tr>
<tr>
<td>d</td>
<td>4-(CH3)2</td>
<td>H</td>
<td>3</td>
<td>94</td>
<td>143-4</td>
<td>Cl7H19NO3O</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>Ph</td>
<td>7</td>
<td>90</td>
<td>88-9</td>
<td>90[7]</td>
</tr>
</tbody>
</table>

In order to ratify the structure (6a-c), these anhydride with hydrazones (5) in acetic acids (table 3). compounds were prepared by the reaction acetic

Table 3. Preparation of N1-acetylphenylhydrazones (6a-e) from Ac2O

<table>
<thead>
<tr>
<th>Compound</th>
<th>G</th>
<th>Y</th>
<th>Reaction time (hr)</th>
<th>Yield%</th>
<th>m.p.(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>3</td>
<td>85</td>
<td>119-120</td>
</tr>
<tr>
<td>b</td>
<td>4-Cl</td>
<td>H</td>
<td>1</td>
<td>81</td>
<td>87-8</td>
</tr>
<tr>
<td>c</td>
<td>4-NO2</td>
<td>H</td>
<td>5</td>
<td>75</td>
<td>164-5</td>
</tr>
<tr>
<td>d</td>
<td>4-(CH3)2</td>
<td>H</td>
<td>1</td>
<td>77</td>
<td>142-3</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>Ph</td>
<td>6</td>
<td>70</td>
<td>86-90</td>
</tr>
</tbody>
</table>

a: To compare melting points with hydrazones obtained from the ketene reaction.

N1-Alkylphenylhydrazones, however, were not reactive toward ketene. Prolong treatment of hydrazone (4a, b, c, e) with ketene led to almost pure starting material.

Experimental Section

Melting points are uncorrected. 1H-NMR spectra were recorded on a Varian T-60 spectrometer. Tetrahydrofuran was dried with sodium and distilled prior to use. Microanalysis were performed by Food Research Institute, Norwich-England. Infrared spectra were recorded using the nujol mull technique on a Beckmann Acculab 3 spectrometer. Mass spectra were taken by varian Mat 311 instrument.

Preparation of N1-alkyl-1-phenylhydrazone(4a-h).

Typical Procedure

Benzaldehyde methyphenydrazone (4a) - To the
solution of sodium amide (2g, 0.05mole) in
50ml) was added benzaldehyde
hydrazone (3a) (3.9g, 0.03 mole) in THF (20ml)
6-8C, when a persistent orange colour
the solution was stirred for one hour and the flue
nitrogen gas was intensified to remove all
ammonium formed in solution. The nitrogen flue, then,
and methyl iodide (8.5g, 0.06mole) in THF
(10ml) was added dropwise to the solution at 10-15C.
At the end of the addition, solution became colourless
and the reaction mixture was stirred at room
temperature for one hour. Water (50ml) was added to
the solution and layers were separated. The organic
layer was dried over sodium sulphate. Filtration and
concentration of the filtrate by cooling gave a white
crystals of (4a) (90%).

Table 4. Spectral data of new compounds (4)

<table>
<thead>
<tr>
<th>Compound</th>
<th>¹H-NMR(DCl3/TMS)</th>
<th>¹H M.S.(70ev)m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>3.29 (s, 3H, N-CH3); 6.7-7.5 (m, 10H)</td>
<td>244(M)+, 111, 77, 51</td>
</tr>
<tr>
<td>4b</td>
<td>3.31 (s, 3H, N=CH3); 7.33-8.30 (m, 10H)</td>
<td>255(M)+, 148, 147, 120, 119, 118</td>
</tr>
<tr>
<td>4c</td>
<td>3.1 (s, 6H, N(CH3)2); 3.45 (s, 3H, N-CH3); 6.7-7.9 (m, 10H)</td>
<td>255(M)+, 106, 77, 42</td>
</tr>
<tr>
<td>4d</td>
<td>2.95 (s, 6H, N(CH3)2); 4.5 (s, 2H, N-CH2); 6.6-7.7 (m, 10H)</td>
<td>279(M)+, 238, 222, 77, 41</td>
</tr>
<tr>
<td>4e</td>
<td>5.1 (m, 1H, CH=CH2); 5.3 (s, 2H, C=CH2); 6.6-7.7 (m, 10H)</td>
<td></td>
</tr>
</tbody>
</table>

Preparation of 1-acetyl-1-phenylhydrazones (6a-e) by
the reaction of ketones with hydrazones (5).

Typical Procedure*
Acetic acid benzilidene phenylhydrazone (6a). -
Ketene gas (produced by pyrolysis of acetone at
700-730C) was passed through the solution of
hydrazone (5a) (1g, 0.05mol) in dichloromethane (30ml)
at room temperature for 4 hours. The solvent was
evaporated in vaccuo. The solid residue was crystallized in
ether to give a pale yellow needles of (6a) (95%).

Table 5. Spectral data for the new compounds (6)

<table>
<thead>
<tr>
<th>Compound</th>
<th>¹H-NMR(DCl3/TMS)</th>
<th>IR (VmaxKBr)</th>
<th>MS(70ev) m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2.53 (s, 3H, N-COCH3); 7.0-7.8 (m, 10H)</td>
<td>230, 1690, 1610, 1390</td>
<td>273(M+), 231, 135, 93, 77, 43, 28.</td>
</tr>
<tr>
<td>b</td>
<td>2.6 (s, 6H, N-COCH3); 8.22 (m, 10H)</td>
<td>3020, 1690, 1580, 1385</td>
<td>285(M+), 194, 135, 92, 77, 43.</td>
</tr>
<tr>
<td>c</td>
<td>2.58 (s, 3H, N-COCH3); 2.97 (s, 6H, J=7Hz, N(CH3)3); 7.5 (m, 10H)</td>
<td>2900-3000, 1690-1610</td>
<td>282(M+), 239, 147, 94, 77, 43, 28</td>
</tr>
</tbody>
</table>
Preparation of 1-acetyl-1-phenylhydrazones (6a-e) by the reaction of acetic anhydride with hydrazones (5).

Typical Procedure:

Acetic acid benzylidene phenylhydrazone (6a). To phenylhydrazone (5a) (1g, 0.005 mol) in glacial acetic acid (10 ml) was added acetic anhydride (1 g, 0.01 mole) at room temperature. The reaction mixture was heated under reflux for 3 hours. The solvent and excess acetic anhydride were evaporated in vacuo and the residue was washed with distilled water (10 ml). The solid was dissolved in ether (20 ml) and sodium sulphate was then added and after stirring for few minutes the solution was collected by filtration. The filtrate was concentrated to 10 ml and cooled in an ice bath to give (6a) as a white crystals (0.65 g, 85%).

* For physical and spectral data see table 3 and 5.

References


6. Cheam. Abs. 34, 1941 (1977)

7. Theibacker W. and Leichtle O. R., Ann., 121, 572 (1951)