Condensation of 3-Aryl-2,4-dicarboethoxy-5-hydroxy-5-methylcyclohexanones with o-Phenylenediamine, Thiourea, α,β-Unsaturated Ketones and Hydrazines

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Reaction of the title compound 1 with o-phenylenediamine afforded either the diazepinones (2) or the amides (3). Treatment of 1 with thiourea gave the thiouracils (4). The indazoles (5) gave diacetyl or diphenylsulphonyl derivatives (6, 7) on treatment with acetic anhydride or benzenesulphonyl chloride, respectively. Condensation of 1 with benzenesulphonhydrazide gave the 2-substituted indazole (8). Michael condensation of 1 with anisalyclohexanone gave 9.

Recently Lai and Bhaduri [1] reported the formation of 3-aryl-2,4-dicarboethoxy-5-hydroxy-5-methylcyclohexanones (1a-d) upon treatment ethyl acetoacetate with aromatic aldehydes. To obtain compounds with potential medicinal activity we studied the behaviour of 1a-d towards o-phenylene-diamine, thiourea and α,β-unsaturated ketones.

Upon treatment of 1a-b with o-phenylenediamine in hot acetic acid, the diazepinones [2] (2a-b) were obtained. Structures 2a-b were assigned from correct analytical data, IR, UV and NMR spectral data. The IR spectra of compounds 2a-b showed absorptions for C=O (amide) at 1650 cm⁻¹, C=O (ester) at 1720 cm⁻¹ and NH stretching at 3100 cm⁻¹. The UV spectrum of compound 2b showed absorption bands at \( \lambda_{\text{max}}^{\text{UV}} \) 258 nm (\( \varepsilon = 5811.1 \)), \( \lambda_{\text{max}}^{\text{UV}} \) 368 nm (\( \varepsilon = 4511.4 \)), \( \lambda_{\text{max}}^{\text{UV}} \) 470 nm (\( \varepsilon = 731.076 \)) and \( \lambda_{\text{max}}^{\text{UV}} \) 498 nm (\( \varepsilon = 674.839 \)). NMR spectrum of compound 2a showed the carboethoxy group protons at (1 ppm, t) for CH₃ (protons a) and (4.1 ppm, q) for CH₂ (protons b). Protons c, d, e, f and h appears at (9.15 ppm, d; 3.15 ppm, t; 2.5 ppm, s; 6 ppm, s; and 4.35 ppm) respectively. The protons g appear at (2.55 ppm, s).

On the other hand, condensation of 1a with o-phenylenediamine at 120-140 °C, lead to the formation of the carboxanilide (3). Cyclization of 3 with hot acetic acid afforded compound 2. The structure of compound 3 was elucidated from its correct elemental analysis, IR and UV spectra. The UV spectrum showed absorption bands at \( \lambda_{\text{max}}^{\text{EIOH}} \) 230 nm (\( \varepsilon = 3488.96 \)), \( \lambda_{\text{max}}^{\text{EIOH}} \) 282 nm (\( \varepsilon = 3027.19 \)) and \( \lambda_{\text{max}}^{\text{EIOH}} \) 370 nm (\( \varepsilon = 1231.40 \)).

The formation of 2a-b is in line with that reported for the reaction of o-phenylenediamine with diethyl 1,4-cyclohexanedione-2,5-dicarboxylate [3].

Treatment of 1a, c and d) with thiourea in ethanolic sodium ethoxide afforded the thiouracil derivatives (4a, c and d) in a good yield. The structure of compounds 4a, c and d) were confirmed by elemental analyses and IR spectra. The IR spectra of 4a, c and d showed two bands at 1385 and 1510 cm⁻¹ (C=S) [4], 1610 cm⁻¹ (CO amide), 1735 cm⁻¹ (CO ester) and broad band at 3100-3300 (NH amide).

\[ a: Ar = C_6H_5; \]
\[ b: Ar = C_6H_4 \cdot CH_3 \cdot p. \]
\[ c: Ar = C_6H_4 \cdot OCH_3 \cdot p; \]
\[ d: Ar = C_6H_4 \cdot N(CH_3)_2 \cdot p. \]
The condensation between 1a-d and hydrazine hydrate to give 4-aryl-5-carboethoxy-6-hydroxy-6-methyl-2,4,5,6,7-tetrahydro-2H-indazoles (5a-d) has been reported [1].

Condensation: 

\[
\begin{array}{c}
\text{5a: Ar = C}_6\text{H}_5; \\
\text{5b: Ar = C}_6\text{H}_4 \cdot \text{CH}_3\cdot \text{p}; \\
\text{5c: Ar = C}_6\text{H}_4 \cdot \text{OCH}_3\cdot \text{p}; \\
\text{5d: Ar = C}_6\text{H}_4 \cdot \text{N(CH}_3)_2\cdot \text{p}. \\
\end{array}
\]

Indazole derivatives (5a-d) may exist in tautomeric forms (i-iii) [1].

\[
\begin{array}{c}
\text{(i)} \\
\text{(ii)} \\
\text{(iii)} \\
\end{array}
\]

Upon treatment of the tetrahydro-2H-indazoles (5a-c) with acetic anhydride, the diacetyl derivatives (6a-c) were obtained. The IR spectra showed absorption bands at 3450 cm\(^{-1}\) (OH), 1785 cm\(^{-1}\) (CO), 1735 cm\(^{-1}\) (CO ester) and 1365 cm\(^{-1}\) (OCOCH\(_3\)). The NMR spectrum of 6a showed the carboethoxy group protons at (0.9 ppm, t) for CH\(_3\) (protons a) and (4 ppm, q) for CH\(_2\) (protons b). Protons c and h appears at (4.8 ppm, s) and (3.15 ppm, d). The ring methylene protons e appears at (1.9 ppm, s). Protons d, i, f and g appears at (1.65 ppm, s; 4.7 ppm, s; 1.9 ppm and 2.45 ppm, s). Similarly condensations of 5a with benzenesulphonyl chloride in pyridine afforded the diphenylsulphonyl derivative (7). Structure 7 was confirmed by analytical data, the IR spectrum and the non identity of 7 with 8, which obtained upon treatment 1a with benzenesulphonhydrazide. The IR spectrum of 7 showed bands assigned to OH (3560 cm\(^{-1}\), CO ester (1725 cm\(^{-1}\), -OSO\(_2\)- (1390 and 1200 cm\(^{-1}\)) and N-\(\text{SO}_2\)- (1340 and 1165 cm\(^{-1}\)).

\[
\begin{array}{c}
\text{6a: Ar = C}_6\text{H}_5; \\
\text{6b: Ar = C}_6\text{H}_4 \cdot \text{CH}_3\cdot \text{p}; \\
\text{6c: Ar = C}_6\text{H}_4 \cdot \text{OCH}_3\cdot \text{p}. \\
\end{array}
\]

Confirmatory evidence for structures 6a-c and 7 is provided by the fact that compound 5 is present in the tautomeric form (iii).

When 1a was treated with anisalicyclohexanone in ethanolic sodium ethoxide, the Michael adduct (9)

\[
\begin{array}{c}
\text{9} \\
\end{array}
\]

was obtained. The structure of compound 9 was elucidated from its correct analysis and IR spectrum.