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# NOTES ON THE REACTIONS OF KETONE ACYLHYDRAZONES UNDER ACYLATION CONDITIONS

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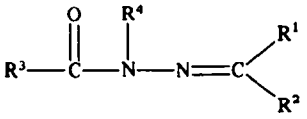
**Abstract**—The reactions of the acetophenone and fluorenone acylhydrazones under acylation conditions were investigated. The structures of the diacylhydrazones and 1,3,4-oxadiazolines formed were proved by UV, IR, $^1$H- and $^{13}$C-NMR spectroscopical as well as by MS evidences. Some results found in the literature are critically discussed.

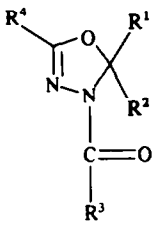
Previously[1] we have described that in certain cases acetylation of aldose acylhydrazones (**1**, $R^1 = R^4 = H$) leads to the formation of 2,3-dihydro-1,3,4-oxadiazoles (**2**, $R^1 = H$, $R^3 = Me$, $R^4 = Me$, Ph) instead of N,N-diacylhydrazones (**1**, $R^4 = Ac$) claimed in the literature. In most cases cyclic derivatives of type **2** are reported[2] to produce from ketone acylhydrazones under similar conditions. However, there are some contradictions concerning the two types of structures when ketone acylhydrazones with bulky groups or aromatic substituents were subjected to such acylation reactions.

The present paper is aimed at a brief discussion of the acylation reaction of some benzophenone and fluorenone acylhydrazones with regard to the above possibilities for the formation of isomers.

Treatment of benzophenone acetylhydrazone (**1a**) with acetyl chloride in the presence of dimethylaniline afforded benzophenone diacetylhydrazone (**1b**), whose structure was proved by its spectroscopic characteristics. Recently Suginome and Uchida[3] have reported on the preparation of **1b** by treatment of benzophenone hydrazone with acetic anhydride. The reported value $\lambda_{max}^{MeOH}$ (ε) 245 (16,000) is very similar to that observed by us, but the reported m.p. 121–124° is remarkably higher than that of our material (m.p. 73°). Repeating the experiment of the above authors the obtained product (**1b**) had a m.p. 73°. When the reaction was performed in hot acetyl chloride we also isolated a product with m.p. 123–125° whose structure we assigned as oxadiazoline **2a** having characteristic UV,



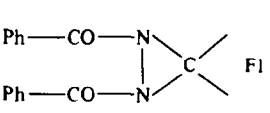
**1**



**2**

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **a** | Ph | Ph | Me | H |
| **b** | Ph | Ph | Me | Ac |
| **c** | Ph | Ph | Ph | H |
| **d** | Ph | Ph | Ph | COPh |
| **e** | Fl | | Ph | H |
| **f** | Fl | | Me | H |
| **g** | Fl | | Me | COPh |
| **h** | Fl | | Ph | COPh |

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **a** | Ph | Ph | Me | Me |
| **b** | Ph | Ph | Me | Ph |
| **c** | Ph | Ph | Ph | Me |
| **d** | Ph | Ph | Ph | Ph |
| **e** | Fl | | Me | Ph |
| **f** | Fl | | Ph | Me |
| **g** | Fl | | Ph | Ph |



**3**

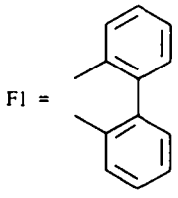


Table 1. Preparation and physical data of **1a, b, 2a, b, d–g**

| Compound | Starting material | | Acylation agent (mol)[a] | Reaction time (temp) | Processing[b] | Yield, % crude (pure) | m.p. (solvent) | Formula (m.w.) | Analysis or MS *m/e* |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | [c] | | $Ac_2O$ (1.4) | 1 hr (100°) | AF | 97(94) | 107–8° (EtOAc)[d] | | |
| **1b** | **1a** | | $AcCl/Me_2NPh$ (8.5; 17) | 42 hr (r.t.) | AF | (80) | 73° (pet. ether) | $C_{17}H_{16}N_2O_2$ (280.32) | 280 (M) |
| **2a** | **1a** | i | $Ac_2O$/TFA (28; 3) | 72 hr (r.t.) and 2 hr (100°) | BDEF | 38.5 | 118° (EtOAc–hexane) | $C_{17}H_{16}N_2O_2$ (280.32) | 280 ($M^+$) |
| | | ii | AcCl (17) | 2 hr (refl.) | BF | (50) | 123–5° (pet. ether) | | |
| **2b** | **1c** | | AcCl (13) | 3 hr (refl.) | BF | (77) | 133° (EtOAc–hexane) | $C_{22}H_{18}N_2O_2$ (342.38) | 342 ($M^+$)[e] |
| **2d** | [c] | | PhCOCl/Py (2; 18) | 20 hr (r.t) | CEF | 81(68) | 128.5° (EtOH–water)[f] | $C_{27}H_{20}N_2O_2$ (404.45) | 404 ($M^+$) |
| **2e** | **1e** | | $AcCl/Me_2NPh$ (8; 18) | 48 hr (r.t.) | AEF | (90) | 188–9° (PhMe–pet. ether) | $C_{22}H_{16}N_2O_2$ (340.37) | 340 ($M^+$) 298 ($M-CH_2CO$) |
| **2f** | **1f** | | PhCOCl/Py (1.1; 18) | 17 hr (r.t.) | CEF | (50) | 128–9° ($CHCl_3$–hexane)[g] | $C_{22}H_{16}N_2O_2$ (340.37) | 340 ($M^+$) |
| **2g** | [h] | | PhCOCl/Py (2; 18) | 16 hr (r.t.) | CEF | 84(74) | 182° (PhH–pet. ether) | $C_{27}H_{18}N_2O_2$ (402.43) | 402 ($M^+$) |

[a] Moles pro mole starting material.
[b] See General methods of preparation (Experimental).
[c] Benzophenone hydrazone.[10]
[d] Lit.[10] m.p. 107° ($Et_2O$) lit.[3] 106–107.5° ($Et_2O$).
[e] Calc: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.58; H, 5.51; N, 8.15.
[f] Lit.[6] m.p. 128.5–129°(EtOH), lit.[5] 131°.
[g] The melt resolidified and had m.p. 185–187°.
[h] Fluorenone hydrazone.

Table 2. UV, IR and NMR spectroscopic characteristics

| Compound | MeOH $\lambda_{max}(\varepsilon)$nm | KBr $\nu_{max}cm^{-1}$ | $^1H$ $\delta$ ($CDCl_3$) ppm | $^{13}C$ $\delta$ ($CDCl_3$) ppm |
|---|---|---|---|---|
| **1a** | 282 (18,600)[a] | 3173 and 3094 (NH)<br>1707, 1678 (amide I)<br>1638 (C=N)<br>1575, 1566 (amide II) | | 172.25 (C=O)<br>149.78 (C=N)<br>20.18 ($\underline{C}H_3$—CO) |
| **1b** | 248 (14,400) | 1717, 1700 (CO.N.CO) | 2.31 (s, 6H, 2Ac) | 176.36 (C=O)<br>169.35 (C=N)<br>25.55 ($\underline{C}H_3$—CO) |
| **2a** | 240 (7400) | 1670 (amide) | 2.27 (s, 3H, Ac)<br>2.13 (s, 3H, O—C($CH_3$)=N) | 166.72 (C=O)[c]<br>153.95 (O—$\underline{C}(CH_3)$=N)[b,c]<br>103.05 (O—$\underline{C}Ph_2$—N)[c]<br>22.80 ($\underline{C}H_3$—CO)[c]<br>11.31 (O—C($\underline{C}H_3$)=N)[b,c] |
| **2b** | 291 (13,800) | 1667, 1641 (amide)<br>1625 (C=N) | 2.39 (s, 3H, Ac) | 167.40 (C=O)<br>153.70 (O—$\underline{C}$Ph=N)<br>103.70 (O—$\underline{C}Ph_2$—N)<br>22.93 ($\underline{C}H_3$—CO) |
| **2d** | 299 (15,000)[d] | 1659 (sh), 1650 (amide)[e]<br>1632 (C=N) | | 164.60 (C=O)[c]<br>154.00 (O—$\underline{C}$(Ph)=N)[c]<br>104.25 (O—$\underline{C}Ph_2$—N)[c] |
| **2e** | | 1677 (amide)<br>1632 (C=N) | 2.34 (s, 3H, Ac) | 165.73 (C=O)[c]<br>155.32 (O—$\underline{C}$(Ph)=N)[c]<br>102.50 (spiro C)[c]<br>22.09 ($\underline{C}H_3$—CO)[c] |
| **2f** | | 1661, 1645 (amide)<br>1611 (C=N) | 2.20 (s, 3H, $CH_3$—C) | 163.09 (C=O)<br>156.34 (O—$\underline{C}(CH_3)$=N)<br>102.45 (spiro C)<br>11.62 (O—C($\underline{C}H_3$)=N) |
| **2g** | | 1640, 1629 (amide)<br>1610 (C=N) | | 162.92 (C=O)<br>155.91 (O—$\underline{C}$Ph=N)<br>103.05 (spiro C) |

[a] Lit.[3] 281 (23,000) nm.
[b] Very similar to that given[4] for the analogous structural unit of dihydrooxadiazolones of similar composition.
[c] At 313 K.
[d] Lit.[6] 300 (17,800) nm.
[e] Lit.[6] 1645 $cm^{-1}$ (amide).

IR, $^1H$- and $^{13}C$-NMR data (Table 2) adequately different from those of compound **1b**. Treatment of **1a** with acetic anhydride in the presence of trifluoroacetic acid gave the same product **2a**.

The reaction of the benzoylhydrazone **1c** with acetyl chloride gave also an oxadiazoline derivative. We have observed earlier[1a] that due to their more pronounced ability for tautomerization aroylhydrazones cyclize more readily into oxadiazolines than acetylhydrazones. Accordingly, the formation of the 3-acetyl isomer **2b** was supposed as more probable than that of the alternative **2c**. In this connection the structure **2b** was justified by the $\delta$ 22.93 ($\underline{C}H_3$—CO) $^{13}C$-NMR signal and also by the *m/e* 300 ($M-CH_2CO$; 42%) fragment in the mass spectrum produced upon loss of ketene.

Reaction of **1c** with benzoyl chloride in pyridine afforded oxadiazoline **2d** which was proved to be identical with that prepared by Stollé[5] by treatment of the silver salt of **1c** with benzoyl chloride in ether. Oxadiazoline **2d** was practically identical with that prepared by Bettinetti and Capretti[6] by the cycloaddition between diphenyldiazomethane and azodibenzoyl. According to our results and to the aforementioned literature[6] data it is surprising that the Fahr group[7] assigned their material produced from **1c** with benzoyl chloride in pyridine, and also the product described by Bettinetti and Capretti as the dibenzoylhydrazone **1d**.

While the reaction of **1a** with acetyl chloride in dimethylaniline gave the corresponding N,N-diacetyl derivative **1b**, under equivalent reaction conditions fluorenone benzoylhydrazone **1e** provided the oxadiazoline derivative **2e**, whose structure was proved principally by the O—$\underline{C}$(Ph)=N and spiro-C $^{13}C$-NMR signals, and by the signal $\delta$ 22.09 ($\underline{C}H_3$—CO) excluding the isomeric structure **2f**. By treatment of **1e** or its silver or potassium salt with acetyl chloride and that of the acetylhydrazone **1f** or its sodium salt with benzoyl chloride Fahr and co-workers obtained identical products (m.p. 185°) whose structure was claimed[8] to be N-acetyl-N-benzoylhydrazone **1g**. On the evidences given above for structure **2e** the conclusions of the Fahr group have to be declared as incorrect. On the other hand these authors claim[8] the product prepared from the sodium salt of acetylhydrazone **1f** with benzoyl chloride in benzene to be hydrazone **1g**, but that from the silver salt of **1f** in ether to be oxadiazoline **2f**. By reacting **1f** itself with benzoyl chloride in pyridine we obtained oxadiazoline **2f** whose structure was unequivocally proved by IR and $^{13}C$-NMR evidences excluding both structures **1g** and **2e**.

Fahr *et al.*[8] characterized oxadiazoline **2f** as thermally unstable transforming into **1g** *via* an

azomethine imine intermediate. We demonstrate (cf. Experimental) this thermic transformation to consist of the conversion of 3-benzoyloxadiazoline **2f** into 3-acetyloxadiazoline **2e** instead of a claimed[8] oxadiazoline → hydrazone (i.e. **2f** → **1g**) isomerization.

The reaction of fluorenone hydrazone with benzoyl chloride in pyridine afforded oxadiazoline **2g**. Fahr *et al.*[7b] declared the dibenzoylhydrazone structure **1h** of the product obtained by treatment of fluorenone hydrazone with benzoyl chloride in pyridine, or the silver or sodium salt of the monobenzoylhydrazone **1e** with benzoyl chloride in benzene or ether. Based on the m.p. and IR spectral data these authors stated that this product **1h** was identical with that prepared by Horner and Lingnau[9] by the cycloaddition reaction between azodibenzoyl and diazofluorenone and declared[9] as a diaziridine derivative **3**. According to our above results with the benzoylation of fluorenone hydrazone it can be established that the correct structure of the product obtained by the Fahr group and by Horner and Lingnau, and characterized as **1h** and **3**, respectively, is really 3 - benzoyl - 2,3 - dihydro - 2 - diphenylene - 5 - phenyl - 1,3,4 - oxadiazole **2g**.

## EXPERIMENTAL

Concerning the starting materials, acylating reagents, reaction conditions, and processing of the reaction mixtures, as well as yields and m.p. data (solvents for recrystallization) see Table 1.

*General methods of preparation*

(A) The reaction mixture was cooled and poured into ice and water. The crude product was further processed by steps F or E and F.

(B) The reaction mixture was concentrated under diminished pressure. The residue was further processed by steps F or D, E and F.

(C) The excess of the acyl halide was decomposed by addition of a little crushed ice under cooling. After *ca* 30 min the mixture was poured into ice and water and the product separated further worked up by steps E and F.

(D) Triturated with ice and water.

(E) Extracted with toluene. The organic layer was washed successively with $KHSO_4$ aq soln (if any base was present), water, $NaHCO_3$ aq soln, and water, treated with anhydrous $MgSO_4$, fuller's earth and activated carbon, and then concentrated under diminished pressure.

(F) Crystallized from the solvent given.

*Isomerization of* **2f** *into* **2e**

Compound **2f** (400 mg, m.p. 128–129°) was heated at 145 ± 2° bath temp for 45 min. The sample became first a yellow oil which resolidified. Recrystallization from $CHCl_3$ (0.8 ml) and hexane (3 ml) afforded **2e** (0.335 g, m.p. 185–187°). On the basis of its IR spectrum the substance was identical with that obtained by treatment of **1e** with acetyl chloride in dimethylaniline.

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