## Condensation of 2-Substituted 5-Oxo-4,5-dihydro-1,3-oxazoles with Imines and Their Corresponding Carbonyl Compounds

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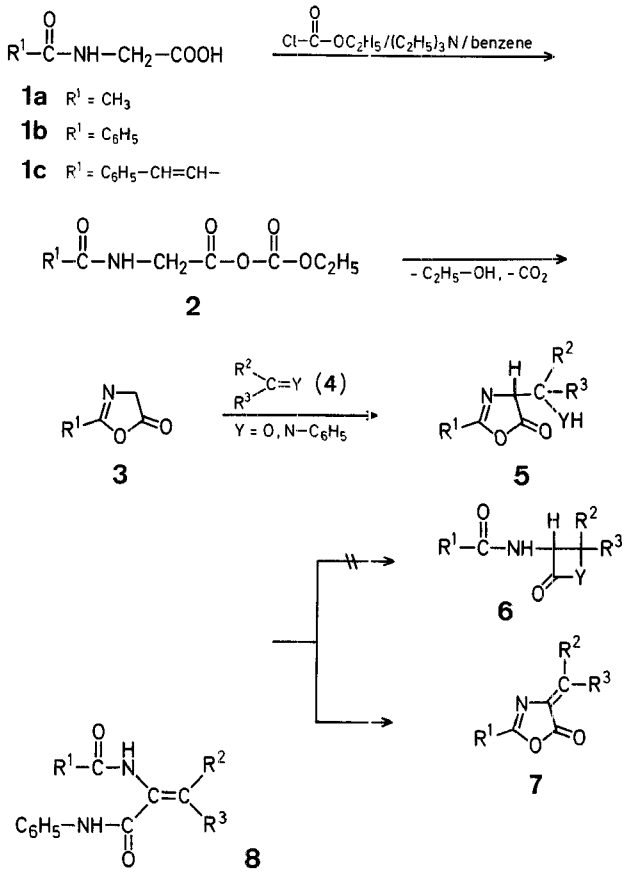
2-Substituted 5-oxo-4,5-dihydro-1,3-oxazoles are important synthetic intermediates and interest in their chemistry continues, as is evidenced by the number of reviews[1-6] on this subject. Recently, some unsaturated 5-oxazolones[7] and the corresponding acyclic derivatives[8] were reported to exhibit anti-cancer activity. Synthesis of these ring systems involves cyclisation of 2-acylamino acids by various reagents, such as acetic anhydride and sodium acetate[1], acetic anhydride and lead acetate[9], polyphosphoric acid[10], sulphur trioxide/dimethyl formamide complex[11], perchloric acid[12,13], and carbodiimides[14,15]. In connection with our studies on β-lactams[16], we investigated some reactions of 5-oxo-1,3-oxazole derivatives[17] and we present here the results of their reaction with imines and the corresponding carbonyl compounds.

*N*-Acylglycines (**1**) were cyclised with ethyl carbonochloridate in the presence of triethylamine in dry benzene and the resultant 5-oxazolones (**3**) were treated with imines (**4**, Y = N—$C_6H_5$). The mixture was gently heated for ~10 min, except in the case of cinnamylideneaniline, for which heating was discontinued after 5 min because of beginning decomposition of the product. On work-up, the expected 4-alkylidene derivatives (**7**) were obtained in moderate to good yields. In some cases, 2-acylamino-2-alkenanilides (**8**) were obtained in very low yield. These products were separated by fractional crystallisation and were characterised by comparison with authentic samples, by microanalyses, and by their spectral data. Their yields depend on the duration of heating. In the ring cleavage of compounds **7** to give **8**, the stereochemistry of the C=C double bond is maintained[18]. It is noteworthy that with 2-methyl-5-oxo-4,5-dihydro-1,3-oxazole (**3a**) only low yields of compounds **7** are obtained due to side reactions.

When carbonyl compounds (**4**, Y = O) were used in place of imines, better or comparable yields of compounds **7** were only obtained in the case of aldehydes. The reaction with cyclohexanone afforded **7j** only in very low yields even after a heating period of ~20 h; a somewhat better yield was obtained when *p*-toluenesulphonic acid was used as a catalyst. Acetophenone failed to react under any of these conditions whereas its *N*-phenylimine reacted to give the expected product (**7i**). It appears that ketones undergo the reaction only reluctantly and that the presence of a catalyst such as metal acetates[18] or tin(IV) chloride[20] or prolonged heating is necessary.

Our present method is simple and the reaction proceeds fast, especially with imines and aldehydes. The conditions



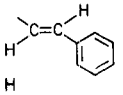
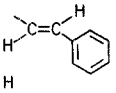
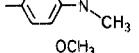
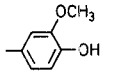
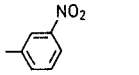
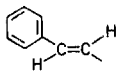

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | $CH_3$ |  | H |
| b |  |  | H |
| c |  |  | H |
| d |  | H |  |
| e |  |  | H |
| f |  |  | H |
| g |  |  | H |
| h |  |  | H |
| i |  |  | $CH_3$ |
| j |  | $-(CH_2)_5-$ | |
| k |  |  | H |

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**Table 1.** Preparation of 2-Substituted 4-Alkylidene-5-oxo-4,5-dihydro-1,3-oxazoles (**7**)

| 7 | Yield [%][a] | | Yields obtained using other Methods | | m.p. [°C] | |
|---|---|---|---|---|---|---|
| | Method A | Method B | Method | Yield [%][b] | found | reported |
| **a** | 14 | 38 | Cyclisation of 2-acylaminocinnamic acid[22] | 74 | 150–151° | 152–153°[22], |
| | | | Erlenmeyer[23,24] | 74–77 | | 148–150°[23,24] |
| **b** | 60 | 77 | Erlenmeyer[25] | 62–64 | 165° | 165–166°[25], |
| | | | Modified Erlenmeyer[c,21] | 63 | | 158°[21] |
| **c** | [d] | | Erlenmeyer[26] | not given | 151° | 152°[26], |
| | | | Modified Erlenmeyer[c,21] | 73 | | 153°[21] |
| **d** | 21 | 58 | Erlenmeyer[5] | 10 | 138–140° | 143°[5] |
| **e**[e] | 86 | 80 | Cyclisation of α-benzoylamino-4-dimethylaminocinnamic acid hydrazide[27] | not given | 213–214°, 215° | 213–214°[27] |
| **f** | 64 | 50 | using $SO_3$-dimethylformamide complex[11] | 66 | 158° | 158°[11] |
| **g** | 60 | 64 | from 5-alkylidene-2-thiohydantoin and 2–4 fold excess of benzoyl chloride in pyridine at reflux (1 h)[28] | 97 | 175–176° | 175–176°[28] |
| | | | Cyclisation of α-benzoylamino-3-nitrocinnamic acid hydrazide[27] | not given | | |
| **h** | 69 | 71 | Modified Erlenmeyer[c,21] | 82 | 168–170° (A), 171–172° (B) | 171°[21] |
| **i** | 42 | | using lead(IV) acetate in boiling tetrahydrofuran (24 h)[19] | 46[f] | 110° | 104°[19] |
| **j** | 50 | 8.4[g], 25[h] | Erlenmeyer[29] | 49 | 137–138° (A), 140° (B) | 137–138°[29] |
| **k** | 61 | 68 | Erlenmeyer[30,31] | 51 | 132–133° (A), 130–132° (B) | 130–133°[30,31] |

[a] Yield of isolated pure product, based on imine or carbonyl compound.

[b] In several cases, we were not able to reproduce the high yields reported in the literature.

[c] In this method, hippuric acid was cyclised with acetic anhydride and the resultant 5-oxazolone was condensed with the carbonyl compound. The configuration was not assigned.

[d] In our method, only the (*E*)-isomer was obtained which during recrystallisation and on prolonged heating was converted into the (*Z*)-isomer with considerable loss of product due to ring cleavage.

[e] The compound is not sufficiently soluble and so its $^1$H-N.M.R. could not be determined. Its configuration is assumed to be *Z* with analogy to products derived from other aromatic aldehydes.

[f] Obtained as (*Z*/*E*)-mixture. Yields of the sterically pure products were not given.

[g] The reaction mixture was heated for 20 h.

[h] The reaction mixture was heated for 20 h and *p*-toluenesulphonic acid was used as a catalyst.

employed are mild and work-up is easy. Some disadvantages of other methods are avoided, e.g., the non-applicability of the cyclisation with acetic anhydride (usual method) to *N*-acylamino acids containing a free hydroxy group (preparation of **7f**), long reaction times in the condensation of compounds **3** with reactants[21], or the necessity of preparing cyclising agents (sulphur trioxide/dimethylformamide complex[11]) before use. The imines used are easily prepared by known methods from aldehydes or ketones and aniline, zinc chloride being used as a catalyst only in the case of ketones. The pure aldimines and ketimines are thus obtained in yields of ~90 and ~55%, respectively. In published methods for the preparation of compounds **7**[5,19], several recrystallisations are necessary to obtain sterically pure products whereas our method affords the sterically pure products directly.

The 2-substituted 4-alkylidene-5-oxo-4,5-dihydro-1,3-oxazoles (**7**) were assigned the (*Z*)-configuration (except for **7d**) on the basis of models constructed by us and in agreement with the $^1$H-N.M.R. spectra and with literature data[5]. Compound **7i** (m.p. 110 °C) has been assigned the (*E*)-configuration on the basis of the methyl signal at $\delta = 2.68$ in the $^1$H-N.M.R. spectrum by Cativiela and Melendez[19]; however, we have found the methyl signal at $\delta = 2.76$ ppm. We ascribe this latter signal to *cis*-disposition of the methyl and carbonyl groups with respect to each other. Rao[10] reported the stereospecific synthesis of (*E*)-**7i** with m.p. 183 °C and a methyl signal at $\delta = 2.6$ ppm. It is noteworthy that the (*Z*)-isomer is stabler than

**Table 2.** Spectral Data of Compounds **7**

| 7 | I.R. (nujol) ν [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/TMS) δ [ppm] |
|---|---|---|
| **a** | 1800, 1770, 1650 | 2.36 (s, 3 H, $CH_3$); 7.14 (s, 1 H, 4-C=CH); 7.4–8.1 (m, 5 $H_{arom}$) |
| **b** | 1790, 1770, 1650 | 7.26 (s, 1 H, 4-C=CH); 7.4–8.1 (m, 10 $H_{arom}$) |
| **c** | 1800, 1790, 1650 | 6.94–7.04 (m, 2 H, =CH—CH=); 7.2–8.2 (m, 10 $H_{arom}$ and 1 H, $C_6H_5$—CH=) |
| **d** | 1800, 1790, 1650 | 7.04–7.14 (m, 2 H, =CH—CH=); 7.3–8.2 (m, 10 $H_{arom}$ and 1 H, $C_6H_5$—CH=) |
| **e** | 1790, 1770, 1770, 1600 | (see footnote of Table 1) |
| **f** | 3400, 1790, 1760, 1660 | 4.08 (s, 3 H, $H_3CO$); 6.94 (s, 1 H, exchangeable, OH); 7.10 (1 H, 4-C=CH); 7.2–8.2 (m, 8 $H_{arom}$) |
| **g** | 1800, 1760, 1660 | 7.42 (s, 1 H, 4-C=CH); 7.8–8.5 (m, 9 $H_{arom}$) |
| **h** | 1790, 1760, 1660 | 6.7 (q, 1 H, 2-furyl-CH); 7.20 (s, 1 H, 4-C=CH); 7.4–8.2 (m, 7 $H_{arom}$) |
| **i** | 1790, 1760, 1640 | 2.76 (s, 3 H, $CH_3$); 7.3–8.2 (m, 10 $H_{arom}$) |
| **j** | 1780, 1750, 1650 | |
| **k** | 1800, 1780, 1640 | 6.8 (d, 1 H, $J = 16$ Hz, $C_6H_5$—CH=CH—); 7.26 (s, 1 H, 4-C=CH); 7.4–7.9 (m, 10 $H_{arom}$); 8.2 (d, 1 H, $J = 16$ Hz, $C_6H_5$—CH=CH) |

**Table 3.** Preparation of *N*-Phenyl-2-acylamino-2-alkenamides (**8**)

| 8 | Yield[a] [%] | m.p. [°C] | Molecular formula[b] or m.p. reported | I.R. (nujol) $\nu$ [cm$^{-1}$] |
|---|---|---|---|---|
| **a** | 67 (4.2) | 187–190° | 188–189°[32] | 3350, 3250, 1670, 1650 |
| **b** | 32 (3.5) | 235–237° | 230–232°[32] | 3300, 1660, 1640 |
| **c** | (not obtained in Method A) | | | |
| **d** | (not obtained in Method A) | | | |
| **e** | (not obtained in Method A) | | | |
| **f** | 35 (10) | 225° | $C_{23}H_{20}N_2O_4$ (388.4) | 3450, 3200, 1660, 1640 |
| **g** | (8) | 223–224° | $C_{22}H_{17}N_3O_4$ (387.4) | 3250, 1670, 1640 |
| **h** | (not obtained in Method A) | | | |
| **i** | 70 (17) | 232° | $C_{23}H_{20}N_2O_2$ (356.4) | 3300, 1660 |
| **j** | 36 | 260° | 245°[33] | 3300, 1660, 1640 |
| **k** | 62 (9) | 232° | 230°[33] | 3300, 3200, 1650, 1610 |

[a] Yields of isolated product obtained using the general procedure. The yields in brackets refer to isolation of compounds **8** as side products when Method A was used.

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.27; H, ±0.39; N, ±0.22.

the (*E*)-isomer and we have found that **7d** is isomerised to **7c** on heating (already during recrystallisation). It is likely that the (*E*)-isomer is initially formed and subsequently isomerised to the (*Z*)-isomer. This point could not be settled since the (*E*)-isomers are elusive under the conditions employed by us.

All melting points are uncorrected. The I.R. and $^1$H-N.M.R. spectra were recorded on Perkin-Elmer 720 and Varian A60 spectrometers, respectively.

**2-Substituted 4-Alkylidene-5-oxo-4,5-dihydro-1,3-oxazoles (7); General Procedures:**

Method A, using Imines: To a suspension of the *N*-acylglycine (**1**; 1.2 mol) in dry benzene (25 ml/g of the acid) containing triethylamine (1.2 mol), ethyl carbonochloridate (1.2 mol) is added and the mixture is shaken at room temperature until the *N*-acylglycine crystals disappear and triethylamine hydrochloride separates. The hydrochloride is removed by suction and washed twice with benzene. The benzene solution and washings are combined and then added to the *N*-phenylimine (**4**, Y = *N*-$C_6H_5$; 1.0 mol) dissolved in dry benzene (5 ml/g of the imine). The mixture is gently heated on a water bath for 5 min in the case of *N*-cinnamylideneaniline and for 10 min in all other cases. The solvent is removed under vacuum to give a pasty mass which on trituration with ethanol gives a solid. This is isolated by suction, washed twice with ethanol, and recrystallised from ethanol.

Method B, using Carbonyl Compounds: To a suspension of the *N*-acylglycine (**1**; 1.0 mol) in dry benzene (25 ml/g of the acid) containing triethylamine (1.5 mol), ethyl carbonochloridate (1.1 mol) is added and the mixture is shaken at room temperature until the *N*-acylglycine crystals disappear and triethylamine hydrochloride separates. The carbonyl compound (**4**, Y = O; 1.0 mol) is added to the mixture which is then heated under reflux for ≈10 min. Triethylamine hydrochloride is removed by suction and washed twice with dry benzene. The benzene solution and washings are combined and concentrated to dryness under reduced pressure. Trituration with ethanol gives a solid which is isolated by suction and washed twice with ethanol. The crude product obtained is sufficiently pure; it may be recrystallised from ethanol.

The *N*-phenyl-2-acylamino-2-alkenamides **8** are formed as by-products in minor amounts when method A is followed. They are isolated by concentrating the ethanolic filtrate and washings and purified by several recrystallisations from ethanol. Compounds **8** may be obtained in preparative yields by the following procedure.

***N*-Phenyl-2-acylamino-2-alkenamides (8); General Procedure:**

A suspension of the 4-alkylidene-5-oxo-4,5-dihydro-1,3-oxazole (**7**) and aniline (molar ratio 1/1) in benzene or ethanol (15 ml/g of **7**) is heated under reflux for 4 h. When benzene is used as solvent the white solid which separates is isolated by suction. When ethanol is used as solvent, the resultant clear solution is concentrated and the residual product recrystallised from ethanol.

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