OXAZOLONES; PART III.[1, 2] REACTION OF 5(4H)-OXAZOLONES WITH HYDRAZONOYL HALIDES: A NEW SYNTHESIS OF 5-PYRAZOLONES

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Abstract - Reaction of 2-(4-methoxyphenyl)-4-phenyl-5(4H)-oxazolone (**1**) with hydrazonoyl chlorides **2** under phase transfer conditions afforded 1,4-diaryl-4-(4-methoxybenzamido)-5(1H)-pyrazolone-3-carboxylic acid alkylesters **3** as the main products. Besides ethanedioic acid monoesters 2-aryl-2-(2,4-diaryl-oxazol-5-yl)hydrazides **4** and 4,4'-bis-(1,2,4-triaryl-5(1H)-imidazolones) **5** were obtained.

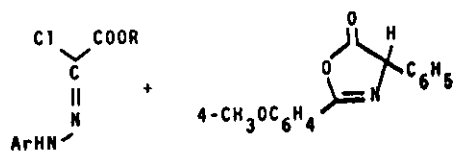
5(4H)-Oxazolones having at least an H-atom on C-4 are well known as precursors of reactive carbanions which can undergo a great number of reactions.[3]

Previous work from our research group dealt with the alkylation and arylation of 5(4H)-oxazolones under phase transfer conditions.[2,4]

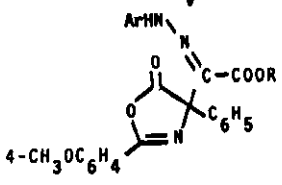
Aiming to extend the potential of 5(4H)-oxazolones as starting compounds for the synthesis of heterocycles and to find a route to substituted pyrazolones for pharmacological evaluation, we have investigated the reaction of 2-(4-methoxyphenyl)-4-phenyl-5(4H)-oxazolone (**1**) with several hydrazonoyl chlorides **2a-n**.

Oxazolone **1** was reacted with an equimolar amount of the corresponding hydrazonoyl chloride **2** in methylene chloride solution in presence of an aqueous solution of sodium carbonate and of a catalytic amount of tetrabutylammonium bromide. The reaction mixture was stirred at room temperature until consumption of the starting compounds and elaborated by column chromatography. As the main products pyrazolones **3a-n** were obtained in 4-47% yield and identified on the basis of analytical and spectroscopic data, mainly IR absorptions in the NH, C=O and C=N regions. An X-ray single-crystal analysis of **3d** confirmed the structure. The formation of compounds **3** is easily rationalized by the nucleo-

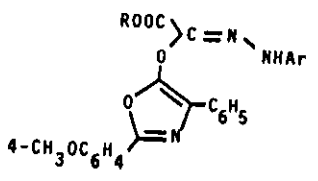
SCHEME



2a-n 1



(a)



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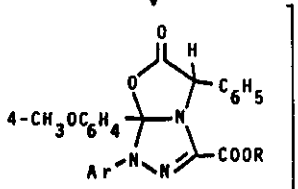

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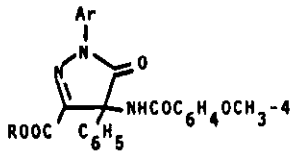
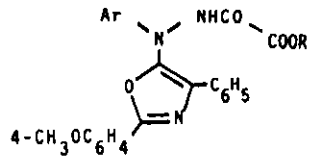
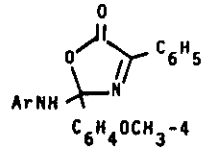


3a-n



4a-c



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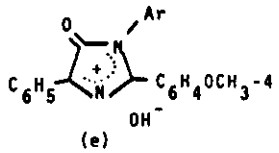

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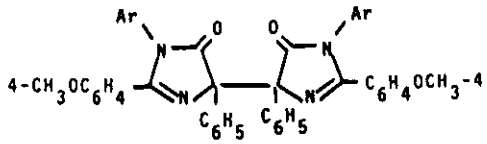


5a-d

3	R	Ar
a	CH_3	$3,4\text{-}Cl_2C_6H_3$
b	CH_3	$3\text{-}ClC_6H_4$
c	CH_3	$3\text{-}CH_3C_6H_4$
d	CH_3	$3,5\text{-}(CF_3)_2C_6H_3$
e	CH_3	$3\text{-}CH_3OC_6H_4$
f	CH_3	$3\text{-}CH_3\text{-}4\text{-}BrC_6H_3$
g	CH_3	$4\text{-}n\text{-}C_3H_7OC_6H_4$
h	C_2H_5	C_6H_5
i	C_2H_5	$4\text{-}CNC_6H_4$
l	CH_3	$3\text{-}CF_3C_6H_4$
m	CH_3	$4\text{-}ClC_6H_4$
n	C_2H_5	$3\text{-}NO_2C_6H_4$

4	R	Ar
a	CH_3	$3\text{-}ClC_6H_4$
b	CH_3	$3,5\text{-}(CF_3)_2C_6H_3$
c	CH_3	$CH_3OC_6H_4$

5	R	Ar
a	CH_3	$3,4\text{-}Cl_2C_6H_3$
b	CH_3	$3\text{-}ClC_6H_4$
c	CH_3	$3,5\text{-}(CF_3)_2C_6H_3$
d	CH_3	$3\text{-}CF_3C_6H_4$
e	CH_3	$4\text{-}ClC_6H_4$

philic attack of the anion derived from **1** to the hydrazonoyl chloride or, possibly, to the corresponding nitrile imine giving intermediate **a** which rearranges to the final product (Scheme). This reaction shows some similarity with the reported pyrazolone formation from oxazolone intermediates having an hydrazinoalkyl substituent.[5]

In some instances, besides **3** the oxazole derivatives **4a-c** and/or the bis-imidazolones **5a-e** were formed in substantial amount and could be isolated. The identification of **4** rests on analytical and spectroscopic evidence, mainly IR absorptions in the COOR and CONH regions and the presence of a typical ^{1}H-NMR signal associated with the NH group in the δ = 9.0-10.0 region. Confirmation was obtained from X-ray analysis of **4b**. Compounds **5** show in the IR spectrum a band indicative of the imidazolone structure[6] at 1740-1750 cm^{-1} and are characterized by an EI-mass spectrum lacking the molecular ion and showing instead a peak with a m/z of half the molecular weight corresponding to the radical originated by cleavage of the band linking the two imidazolone moieties. FD-mass spectrum allowed to evidence the molecular ion. The easy thermal cleavage of bis-azolone compounds has been observed in other instances.[7]

An explanation of the reaction pathways which afford products **4** and **5** is indicated in the Scheme. Through the acylation of the enolate of **1** by the halide **2** intermediate **b** is produced which is transformed into the final product **4** by the well known intramolecular rearrangement of arylhydrazonate esters.[8, 9]

Through cycloaddition of the nitrile imine intermediate deriving from **2**, adduct **c** is obtained[10, 11] which can rearrange to the pseudobase **e** by cleavage of the triazole ring (cyanoformate elimination[12]) and Dimroth-type rearrangement of **d**. Reduction of **e** gives the corresponding radical which dimerizes to **5**. The formation of bis-imidazolones from the corresponding radicals is known.[13]

Alternative mechanisms as the formation of **5** from the bis-oxazolone which is known to be oxidatively originated from **1** under basic conditions[14] or from an open chain intermediate as the corresponding N-(4-methoxybenzoyl)-phenylglycine-anilide could be excluded by separate experiments under the same conditions. It was also ruled out that **3, 4** or **5** could be the precursors of another of the products since they were stable under the reaction conditions.

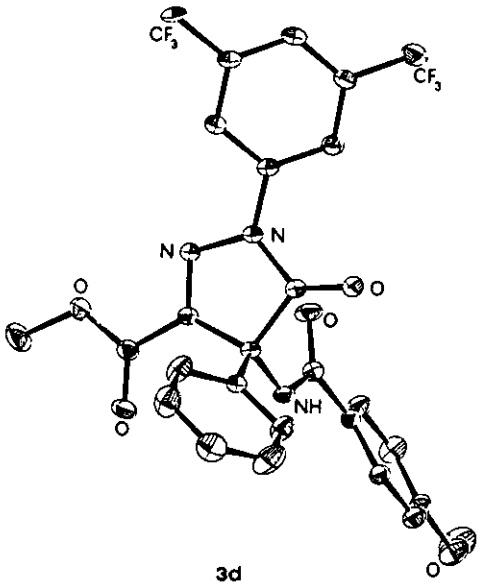
Unit-cell dimensions and X-ray diffracted intensity data for compounds **3d, 4b** and **5c** were measured at room temperature on an Enraf-Nonius CAD4 diffractometer equipped with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods with program MULTAN[15] and refined by least-squares methods using the SDP-Plus program package.[16]

Compound **3d**, $C_{27}H_{19}N_3O_5F_6$, crystallizes in the triclinic space group $P\bar{1}$ whith a = 9.359(1), b = 10.194(2), c = 15.693(3) Å, α = 100.41(2), β = 101.25(2), γ = 110.17(2)°, V = 1327.4(5)Å^3, Z = 2, D_x = 1.450 g/cm^3. 4649 independent reflections were measured up to 2θ = 50° by the ω-scan technique. For 2937 reflections with I > 2σ(I) the R and wR values are 0.061 and 0.064, respectively. A drawing of the molecule, with thermal ellipsoids at the 0.20 probability level, is reported in the Figure, where the H atoms have been omitted for the sake of clarity. The F atoms of the two $-CF_3$ groups, affected by very high thermal motion and/or disorder, are also omitted. The pyrazolone ring shows a slight twist conformation with axis through the N atom involved in the C=N double bond; the puckering parameters[17] are q_2 = 0.086 Å and ψ_2 = 270.3°. The $-COOCH_3$ group is almost coplanar with the five-membered ring, the dihedral angle between the two corresponding planes being ~2°. Bond distances and angles do not show unusual values.

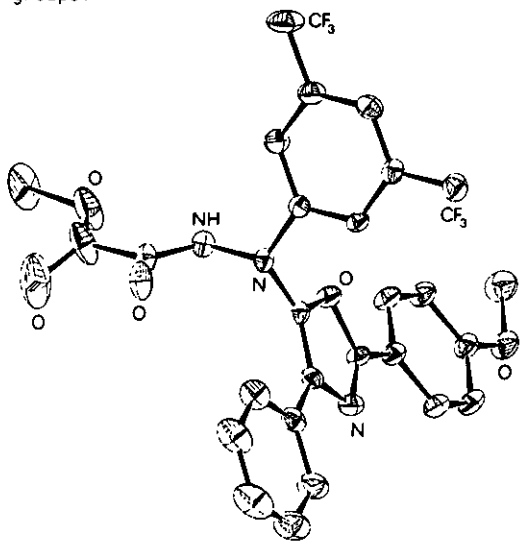
The crystals of compound **4b** are tetragonal, space group $I4_1/a$, with a = 25.751(7), c = 15.981(4) Å, V = 10597(5) Å^3, Z = 16, D_x = 1.453 g/cm^3. Least-squares refinement was hampered by extensive disorder affecting one of the two $-CF_3$ groups and the $-COOCH_3$ fragment. The presence of disorder was also reflected in the large number of weak intensities: out of the 4730 independent reflections collected by θ:2θ scans within 2θ<50°, only 3170 had net intensity I > σ(I). The molecular model reported in the Figure gave R = 0.065 and wR = 0.080 on the 1315 reflections with I>2σ(I) and (sinθ/λ)<0.42. The five atoms of the oxazole ring are coplanar within 0.004 Å. Their plane makes a dihedral angle of ~3° with that of the phenyl ring with no substituents, and of ~11° with the plane of the ring carrying the $-OCH_3$ group.

Bis-imidazolone **5c** crystallizes as a CH_3CN solvate in triclinic space group $P\bar{1}$, with a = 8.758(3), b = 16.150(4), c = 16.524(4) Å, α = 91.10(2), β = 94.98(2), γ = 95.42(2)°, V = 2317(1) Å^3. With two units of formula $C_{48}H_{30}N_4O_4F_{12}\cdot CH_3CN$ per cell, D_x is 1.427 g/cm^3 versus 1.415 g/cm^3 measured. Within the limit of 2θ<45°, 6029 independent reflections were measured. The least-squares refinement of the structure, based on the 4814 F_{obs} whose net intensities were above background (I>0), gave R = 0.096 and wR = 0.059. A drawing of one of the two crystallographically independent molecules of **5c** included in the cell is given in the Figure. As shown by the Figure, the molecule is made of two imidazolone moieties related by a center of symmetry. The lenght of the C-C bond which connects the two halves of the molecule is 1.602(5)Å in one molecule and 1.594(4)Å in the other. These values are similar to those found in multi-substituted ethanes, e.g. 1.606(3)Å for the central bond of pentaphenylethane.[18] The conformation of the two molecules is very similar, most of their

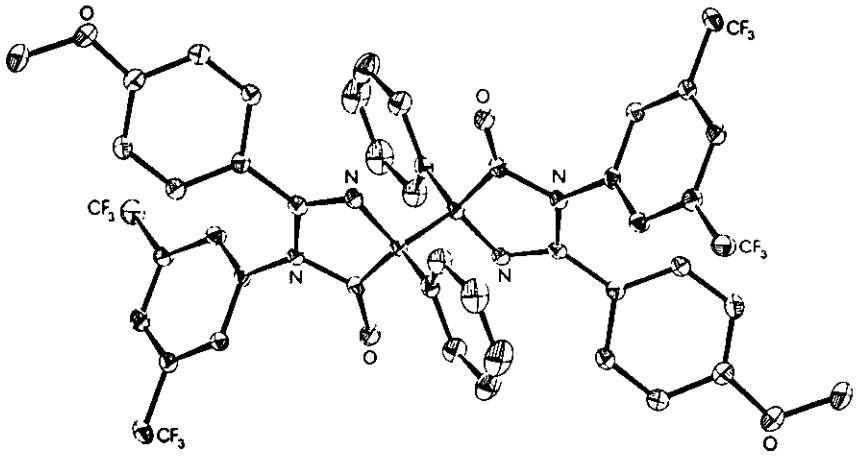
corresponding dihedral and torsion angles differing by less than 10°. Larger differences are found between the relative orientations of the $-CF_3$ and $-OCH_3$ groups.[19]



3d



4b



5c

Figure. Perspective views of molecules **3d**, **4b** and 5c as determined by X-ray analysis. H and F atoms have been omitted for the sake of clarity.

EXPERIMENTAL

Oxazolone **1** was prepared according to a literature procedure,[14] hydrazonoyl chloride **2a-e, g-h, l-n**[20] are known compounds. New compounds **2f** and **2i** were obtained according to the same method: **2f**, mp 150-151°C; (yield: 86%); **2i**, mp 178°C; (yield: 90%).

Table. Pyrazolones **3**, Oxazoles **4**, and Imidazolones **5** Prepared

Compd. No.	Eluent[a]	Yield[b]	mp (°C)[c] (solvent)	Molecular[d] formula	(Nujol)[e] ν(cm^{-1}) NH	C=O	C=N	^{1}H-NMR ($CDCl_3$/TMS)[f] δ ppm
3a	1/3	37	168-169 (CH_2Cl_2/(i-C_3H_7)$_2$O)	$C_{25}H_{19}Cl_2N_3O_5$ (512.3)	3360	1740, 1710 1670	1610	3.8, 3.9 (two s, 6H, OCH_3); 6.9-7.9 (m, 13H, H_{arom} and NH)
3b	CH_2Cl_2	27	154 ($CHCl_3$/(i-C_3H_7)$_2$O)	$C_{25}H_{20}ClN_3O_5$ (477.9)	3340	1730, 1700 1670	1605	3.8, 3.9 (two s, 6H, OCH_3); 6.8-7.9 (m, 14H, H_{arom} and NH)
3c	1/1	44	108-110 ($CHCl_3$/(i-C_3H_7)$_2$O)	$C_{26}H_{23}N_3O_5$ (457.5)	3350	1740, 1690 1670	1610	3.8, 3.9 (two s, 6H, OCH_3), 6.7-7.9 (m, 14H, H_{arom} and NH)
3d	1/2	9	218-219 (CH_2Cl_2/n-C_5H_{12})	$C_{27}H_{19}F_6N_3O_5$ (579.4)	3380	1755, 1720 1650	1610	3.8, 3.9 (two s, 6H, OCH_3); 6.7-7.8 (m, 11H, H_{arom} and NH); 8.5 (s, 2 H_{arom})
3e	CH_2Cl_2	46	136-139 ($CHCl_3$/(i-C_3H_7)$_2$O)	$C_{26}H_{23}N_3O_6$ (473.5)	3340	1735, 1700 1660	1610	3.7, 3.8, 3.9 (three s, 9H, OCH_3); 6.7-7.9 (m, 14H, H_{arom} and NH)
3f	1/3	27	185 dec. (CH_2Cl_2/(i-C_3H_7)$_2$O)	$C_{26}H_{22}BrN_3O_5$ (536.4)	3340	1730 1700 1660	1610	2.4 (s, 3H, CH_3); 3.8, 3.9 (two s, 6H, OCH_3); 6.7-7.9 (m, 13H, H_{arom} and NH)
3g	1/5	16	161-162 ($CHCl_3$/(i-C_3H_7)$_2$O)	$C_{28}H_{27}N_3O_6$ (501.5)	3280	1740, 1685 1665	1610	1.0 (t, J = 6 Hz, 3H, CH_3); 1.4-1.9 (m, 2H, CH_2); 3.6-4.0 (m, 8H, OCH_3 and OCH_2); 6.7-7.9 (m, 14H, H_{arom} and NH)
3h	CH_2Cl_2	27	136-138 ($CHCl_3$/(i-C_3H_7)$_2$O)	$C_{26}H_{23}N_3O_5$ (475.5)	3320	1730, 1710 1665	1610	1.3 (t, J = 6 Hz, 3H, CH_3); 3.8 (s, 3H, OCH_3); 4.3 (q, J = 6 Hz, 2H, OCH_2); 6.7-7.9 (m, 15H, H_{arom} and NH
3i	2/1	40	199-200 ($CHCl_3$, hot)	$C_{27}H_{22}N_4O_5$ (482.5)	3380	1730, 1710 1650	1610	1.3 (t, J = 6 Hz, 3H, CH_3); 3.8 (s, 3H, OCH_3); 4.3 (q, J = 6 Hz, 2H, OCH_2); 6.7-7.9 (m, 14H, H_{arom} and NH

3l	1/1	4	168-170 ($CHCl_3$/$(i\text{-}C_3H_7)_2O$)	$C_{26}H_{20}F_3N_3O_5$ (511.4)	3380	1740, 1700 1655	1605	3.8, 3.9 (two s, 6H, OCH_3); 6.9-7.9 (m, 14H, H_{arom} and NH)
3m	CH_2Cl_2	25	130 (CH_2Cl_2/$(i\text{-}C_3H_7)_2O$)	$C_{25}H_{20}ClN_3O_5$ (477.9)	3340	1735, 1700 1660	1605	3.9, 4.0 (two s, 6H, OCH_3); 6.8-7.9 (m, 14H, H_{arom} and NH)
3n	1/5	20	153-155 ($CHCl_3$/$(i\text{-}C_3H_7)_2O$)	$C_{26}H_{22}N_4O_7$ (502.47)	3320	1740, 1700 1670	1600	1.4 (t, J = 6 Hz, 3H, CH_3); 3.9 (s, 3H, OCH_3); 4.4 (q, J = 6 Hz, 2H, OCH_2); 6.8-8.2 (m, 13H, H_{arom} and NH); 8.4 (s, $1H_{arom}$)
4a	1/3	15	115-116 (CH_2Cl_2/$n\text{-}C_5H_{12}$)	$C_{25}H_{20}ClN_3O_5$ (477.9)	3320	1740, 1720	1610	3.7, 3.8 (two s, 6H, OCH_3); 6.6-8.1 (m, $13H_{arom}$); 9.2 (s, 1H, NH)
4b	1/1	10	165-166 dec. (CH_2Cl_2/$n\text{-}C_5H_{12}$)	$C_{27}H_{19}F_6N_3O_5$ (579.4)	3280	1765, 1705	1610	3.8, 3.9 (two s, 6H, OCH_3); 6.8-8.2 (m, $12H_{arom}$); 9.4 (s, 1H, NH)
4c	1/3	2	127-128 ($CHCl_3$/$(i\text{-}C_3H_7)_2O$)	$C_{26}H_{23}N_3O_6$ (473.5)	3320	1730, 1710	1600	3.6, 3.7, 3.8 (three s, 9H, OCH_3); 6.3-8.3 (m, $13H_{arom}$); 9.5 (s, 1H, NH
5a	1/3	35	275-276 dec. ($CHCl_3$, hot)	$C_{44}H_{30}Cl_4N_4O_4$ (820.6)		1750	1620	3.8 (s, 3H, OCH_3); 6.7-8.1 (m, 12 H_{arom})
5b	1/3	4	279-280 dec. ($CHCl_3$, hot)	$C_{44}H_{32}Cl_2N_4O_4$ (751.6)		1745	1620	3.8 (s, 3H, OCH_3); 6.7-8.1 (m, 13 H_{arom})
5c	1/2	11	253-254 dec. ($CHCl_3$/$n\text{-}C_5H_{12}$)	$C_{48}H_{30}F_{12}N_4O_4$ (954.7)		1750	1610	3.8 (s, 3H, OCH_3); 6.7-8.2 (m, 12 H_{arom})
5d	4/1	5	272-274 dec. ($CHCl_3$, hot)	$C_{46}H_{32}F_6N_4O_4$ (818.7)		1740	1620	3.8 (s, 3H, OCH_3); 6.7-8.1 (m, 13 H_{arom})
5e	CH_2Cl_2	10	264-265 dec. ($CHCl_3$, hot)	$C_{44}H_{32}Cl_2N_4O_4$ (751.6)		1740	1610	3.8 (s, 3H, OCH_3); 6.7-8.1 (m, 13 H_{arom})

a) Ratio of eluent (petroleum ether/dichlorometane) in column chromatography.

b) Not optimized.

c) Uncorrected, measured with a Büchi 510 apparatus.

d) Microanalyses data for new compounds:

3a C, 58.61; H, 3.74; N, 8.20 (C, 58.26; H, 3.62; N, 8.14).

3b C, 62.83; H, 4.22; N, 8.79 (C, 62.54; H, 4.08; N, 8.86).

3c C, 68.25; H, 5.06; N, 9.18 (C, 67.88; H, 5.21; N, 9.13).

3d C, 55.96; H, 3.30; N, 7.25 (C, 56.30; H, 3.26; N, 7.27).

3e C, 65.95; H, 4.89; N, 8.87 (C, 65.50; H, 4.68; N, 8.62).

3f C, 58.21; H, 4.13; N, 7.83 (C, 57.86; H, 4.08; N, 7.69).

3g C, 67.05; H, 5.43; N, 8.38 (C, 66.79; H, 5.07; N, 8.03).

3h C, 68.25; H, 5.06; N, 9.18 (C, 67.85; H, 4.88; N, 8.96).

3i C, 67.21; H, 4.59; N, 11.61 (C, 66.79; H, 4.38; N, 11.43).

3l C, 61.05; H, 3.94; N, 8.21 (C, 60.76; H, 3.93; N, 7.74).

3m C, 62.83; H, 4.22; N, 8.79 (C, 62.53; H, 4.15; N, 8.95).

3n C, 62.14; H, 4.41; N, 11.15 (C, 61.75; H, 4.45; N, 10.95).

4a C, 62.83; H, 4.22; N, 8.79 (C, 62.46; H, 4.22; N, 8.56).

4b C, 55.96; H, 3.30; N, 7.25 (C, 55.59; H, 3.44; N, 7.09).

4c C, 65.95; H, 4.89; N, 8.87 (C, 65.53; H, 4.90; N, 8.78).

5a C, 64.39; H, 3.68; N, 6.82 (C, 64.59; H, 3.60; N, 7.19).

5b C, 70.31; H, 4.29; N, 7.45 (C, 69.85; H, 4.25; N, 7.48).

5c C, 60.38; H, 3.16; N, 5.87 (C, 60.73; H, 3.25; N, 5.77).

5d C, 67.47; H, 3.94; N, 6.84 (C, 67.29; H, 4.04; N, 6.74).

5e C, 70.30; H, 4.29; N, 7.45 (C, 69.92; H, 4.53; N, 7.38).

e) Recorded on a Perkin-Elmer 197 Infrared spectrophotometer.

f) Obtained on a Varian EM 360, 60 MHz spectrometer. DMSO-d_6/TMS_{int} as solvent for **5a,b,d,e**. ^{13}C-NMR (Varian XL-200, $CDCl_3$/TMS_{int} as solvent): **3d**: δ = 52.9 ($\underline{C}H_3OCO$); 55.5 (CH_3O); 66.8 (C-4); 159.7 (C-3); 166.9 ($\underline{C}OOCH_3$ and CONH); 170.5 (C-5). **4b**: δ = 53.9 ($\underline{C}H_3OCO$); 55.3 (CH_3O); 138.7 (C-5); 155.1 (C-2); 159.8 (CONH); 167.3 (COO). **5c**: δ = 55.3 (CH_3O); 79.2 (C-4); 159.1 (C-2); 177.4 (C-5). MS (Varian MAT-311-A, 70eV): **3c**: (EI), $\underline{m/z}$ = 457 (M^+). **3d**: (EI), $\underline{m/z}$ = 579 (M^+, 2). 135 (100). **4b**: (EI), $\underline{m/z}$ = 579 (M^+,1), 134 (100). **5a**: (FD), $\underline{m/z}$ = 818 (M^+), 409. **5b**: (FD), $\underline{m/z}$ = 375. **5c**: (FD), $\underline{m/z}$ = 954 (M^+); (EI), $\underline{m/z}$ = 477 (33), 346 (100). **5d**: (FD), $\underline{m/z}$ = 409.

Pyrazolones 3a-n, Oxazoles 4a-c and Bis-imidazolones 5a-e; General Procedure:

Dichloromethane (35 ml) is mixed with a solution of sodium carbonate (3 g, 30 mmol) in water (25 ml) To the biphasic mixture hydrazonoyl chloride **2** (10 mmol), oxazolinone **1** (2.7 g, 10 mmol), and tetrabutylammonium bromide (0.3 g, 1 mmol) are added. The mixture is vigorously stirred at room temperature until consumption of the starting materials (2-4 h). The organic layer is separated and the

aqueous layer extracted with dichloromethane (20 ml). The combined organic extracts are washed with water until neutral, dried with anhydrous sodium sulfate, and evaporated. The residue is chromatographed on a silica gel column. Petroleum ether (b.p. 40-60°C) is used as eluent which is gradually mixed with dichloromethane. The mixing ratios corresponding to the elution of the products are listed in the Table. The single fractions are crystallized from the solvent indicated in the Table. Yields, mp and analytical data are listed in the Table.

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