# Synthesis of Pyrazoles and Oxyquinoxalines from 2,4-Dioxohexenoates

*H. El Khadem*

Department of Chemistry and Chemical Engineering,
Michigan Technological University, Houghton, Michigan 49931

and

*Zaki El-Shafei, Latif Rateb and Hassan Mokhtar*

Department of Chemistry, Faculty of Science,
Alexandria University, Alexandria, Egypt

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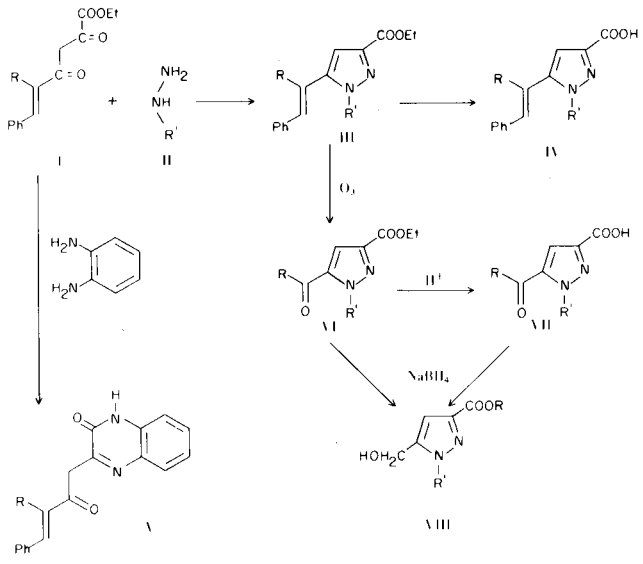
Condensation of ethyl 2,4-dioxo-6-phenylhex-5-enoates (I; R = H, I; R = Me, I, R = Ph) with various hydrazines yielded ethyl 5-styrylpyrazole-3-carboxylates (III), which were hydrolyzed to the acids (IV), and ozonized to 5-keto pyrazole esters (VI) and acids (VII). Reduction of the 5-formylpyrazoles (VI; R = H) with borohydride afforded the 5-hydroxymethyl derivatives (VIII). The same 2,4-dioxohexenoates (I) when treated with *o*-phenylenediamine gave 2-oxyquinoxalines (V; R = H, V; R = Me, V; R = Ph). The uv spectra data of these compounds are given.

Electrophilic substitution in the pyrazole ring occurs preferentially in the 4-position (1). Accordingly, the synthesis of 5-substituted pyrazoles must involve the use of reagents capable of cyclization that possess either the desired substituent or substituents which can subsequently lead to it. Among such reagents are the 2,4-dioxo-6-phenylhex-5-enoates and their 5-substituted derivatives (2-4) which yield with hydrazine ethyl-5-styryl pyrazole-3-carboxylates. The styryl group in such pyrazoles can readily be converted by ozonization to a carbonyl group, then either be reduced to an alcohol or oxidized to an acid. Furthermore, the carboxylate group in position 3- may be used for further condensations or eliminated by hydrolysis and decarboxylation. The present work is part of a study (5,6) to explore the synthetic possibilities of these 2,4-hexenoates; described here is the synthesis of more than forty new pyrazoles and oxyquinoxalines obtained by cyclization with hydrazines and *o*-phenylenediamine, respectively.



Condensation of ethyl 2,4-dioxo-6-phenylhex-5-enoates (I; R = H) and ethyl 2,4-dioxo-5-methyl-6-phenylhex-5-enoate (I, R = Me) and ethyl 2,4-dioxo-5,6-phenylhex-5-enoate (I; R = Ph) with hydrazine hydrate afforded ethyl 5-styrylpyrazole-3-carboxylate (III; R = R′ = H), ethyl 5-(α-methylstyryl)pyrazole-3-carboxylate (III; R = Me, R′ = H) and ethyl 5-(α-phenylstyryl)pyrazole-3-carboxylate (III; R = Ph, R′ = H), respectively. It is interesting to note that during the condensation with acylhydrazines such as acetylhydrazine, benzoylhydrazine or semicarbazide, the CONH bond in the hydrazines is broken and 5-styryl-3-carbethoxystyrylpyrazole (III; R = R′ = H) is obtained. To obtain the corresponding 1-acylpyrazoles, acetylation of the heterocycle must be carried out after the pyrazole is formed. Condensation of 2,4-dioxohexenoates (I; R = Me and I; R = Ph) with *p*-tolyl, *p*-chlorophenyl, *p*-bromophenyl and *p*-nitrophenyl hydrazines afforded the corresponding 5-styrylpyrazole-3-carboxylates (III) (see Table I). Although the reaction of 2,4-dioxohexenoates with assymetric hydrazines can theoretically lead to two isomers, only the 1-aryl-5-styrylpyrazole-3-carboxylate is obtained. The structure of the 1-phenyl isomer was previously established (5,6) by oxidation to the known 1-phenylpyrazole-3,4-dicarboxylic acid. Hydrolysis of

TABLE I

3-Carbethoxy-5-styrylpyrazoles (III)

| Compound No. | R | R′ | Reflux Time, Hours | Yield % | M.p.° | Formula | Analyses Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | 2 | 48 | 142 | $C_{14}H_{14}N_2O_2$ | 69.4 | 5.8 | 11.6 | 69.8 | 5.8 | 11.9 |
| 2 | Me | H | 2 | 92 | 133 | $C_{15}H_{16}N_2O_2$ | 70.0 | 6.2 | 10.9 | 70.0 | 6.3 | 10.9 |
| 3 | Ph | H | 2 | 71 | 208 | $C_{20}H_{18}N_2O_2$ | 75.5 | 5.7 | 8.8 | 75.3 | 5.9 | 9.0 |
| 4 | Me | *p*-$MeC_6H_4$ | 2.5 | 90 | 77 | $C_{22}H_{22}N_2O_2$ | 76.3 | 6.4 | 8.1 | 76.2 | 6.1 | 8.6 |
| 5 | Me | *p*-$ClC_6H_4$ | 2.5 | 81 | 110 | $C_{21}H_{19}ClN_2O_2$ | 68.8 | 5.2 | 7.6 | 69.1 | 5.4 | 7.9 |
| 6 | Me | *p*-$BrC_6H_4$ | 2.5 | 87 | 109 | $C_{21}H_{19}BrN_2O_2$ | 61.3 | 4.6 | 6.8 | 61.1 | 4.7 | 7.1 |
| 7 | Me | *p*-$NO_2C_6H_4$ | 2.5 | 90 | 120 | $C_{21}H_{19}N_3O_4$ | 66.8 | 5.1 | 11.1 | 67.4 | 5.4 | 11.6 |
| 8 | Ph | *p*-$MeC_6H_4$ | 3 | 62 | 152 | $C_{27}H_{24}N_2O_2$ | 79.4 | 5.9 | 6.9 | 79.3 | 5.6 | 6.9 |
| 9 | Ph | *p*-$ClC_6H_4$ | 3 | 52 | 144 | $C_{26}H_{21}ClN_2O_2$ | 72.8 | 4.9 | 6.5 | 73.0 | 5.1 | 6.6 |
| 10 | Ph | *p*-$BrC_6H_4$ | 3 | 75 | 143 | $C_{26}H_{21}BrN_2O_2$ | 66.0 | 4.4 | 5.9 | 65.7 | 4.5 | 6.1 |

TABLE II

5-Styrylpyrazole-3-carboxylic Acids (IV) and 5-Carbonylpyrazole-3-carboxylic Acids (VII)

| Compound No. | Formula | R | R′ | Reflux Time, Hours | M.p.° | Formula | Analyses Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | IV | H | H | 5 | 279 | $C_{12}H_{10}N_2O_2$ | 67.3 | 4.7 | 13.1 | 66.9 | 4.6 | 12.9 |
| 12 | IV | Me | H | 5 | 243 | $C_{13}H_{12}N_2O_2$ | 68.4 | 5.3 | 12.3 | 68.5 | 5.2 | 12.5 |
| 13 | IV | Ph | H | 5 | 277 | $C_{18}H_{14}N_2O_2 \cdot 0.5\,H_2O$ | 72.2 | 5.0 | 9.4 | 72.0 | 4.6 | 9.6 |
| 14 | IV | Me | Ph | 6 | 161 | $C_{19}H_{16}N_2O_2$ | 75.0 | 5.3 | 5.2 | 74.6 | 5.4 | 9.7 |
| 15 | IV | Ph | Ph | 6 | 122 | $C_{24}H_{18}N_2O_2$ | 78.7 | 5.0 | 7.7 | 79.0 | 5.4 | 7.5 |
| 16 | VII | H | Ph | 8 | 158 | $C_{11}H_8N_2O_3$ | 61.1 | 3.7 | 12.9 | 61.0 | 3.8 | 13.0 |
| 17 | VII | H | *p*-$MeC_6H_4$ | 8 | 190 | $C_{12}H_{10}N_2O_3$ | 62.6 | 4.4 | 12.2 | 62.5 | 4.2 | 12.5 |
| 18 | VII | H | *p*-$ClC_6H_4$ | 8 | 220 | $C_{11}H_7ClN_2O_3$ | 52.7 | 2.8 | 11.2 | 52.3 | 3.1 | 11.3 |
| 19 | VII | H | *p*-$BrC_6H_4$ | 8 | 215 | $C_{11}H_7BrN_2O_3$ | 44.7 | 2.4 | 9.5 | 44.4 | 2.6 | 9.6 |
| 20 | VII | H | *p*-$IC_6H_4$ | 8 | 220 | $C_{11}H_7IN_2O_3$ | 38.6 | 2.0 | 8.2 | 38.7 | 2.4 | 7.9 |
| 21 | VII | H | *p*-$NO_2C_6H_4$ | 15 | 248 | $C_{11}H_7N_3O_5$ | 50.6 | 2.7 | 16.1 | 50.2 | 3.1 | 15.8 |
| 22 | VII | Me | *p*-$MeC_6H_4$ | 3 | 180 | $C_{13}H_{12}N_2O_3$ | 63.9 | 5.0 | 11.5 | 63.9 | 4.8 | 11.8 |
| 23 | VII | Me | *p*-$ClC_6H_4$ | 5 | 215 | $C_{12}H_9ClN_2O_3$ | 54.5 | 3.4 | 10.58 | 54.9 | 3.2 | 10.04 |
| 24 | VII | Me | *p*-$BrC_6H_4$ | 4 | 201 | $C_{12}H_9BrN_2O_3$ | 46.7 | 2.9 | 9.1 | 46.7 | 3.2 | 9.6 |
| 25 | VII | Me | *p*-$BrC_6H_4$ | 4 | 239 | $C_{12}H_9O_5 \cdot H_2O$ | 49.2 | 3.8 | 14.3 | 49.1 | 3.7 | 14.2 |
| 26 | VII | Ph | *p*-$MeC_6H_4$ | 12 | 210 | $C_{18}H_{14}N_2O_3$ | 70.6 | 4.6 | 9.2 | 70.9 | 4.7 | 9.3 |
| 27 | VII | Ph | *p*-$ClC_6H_4$ | 12 | 215 | $C_{17}H_{11}ClN_2O_3$ | 62.5 | 3.4 | 8.6 | 63.0 | 3.5 | 8.7 |
| 28 | VII | Ph | *p*-$BrC_6H_4$ | 12 | 218 | $C_{17}H_{11}BrN_2O_3$ | 55.0 | 3.0 | 7.6 | 55.4 | 3.0 | 7.7 |

TABLE III

5-Acetyl- and 5-Benzoylpyrazole-3-carboxylates (VI)

| Compound No. | R | R′ | Yield % | M.p.° | Formula | Analyses Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 29 | Me | *p*-$MeC_6H_4$ | 60 | 124 | $C_{15}H_{16}N_2O_3$ | 66.2 | 5.9 | 10.3 | 65.9 | 5.9 | 10.6 |
| 30 | Me | *p*-$ClC_6H_4$ | 87 | 160 | $C_{14}H_{13}ClN_2O_3$ | 57.4 | 4.5 | 9.6 | 57.6 | 4.5 | 9.6 |
| 31 | Me | *p*-$BrC_6H_4$ | 92 | 163 | $C_{14}H_{13}BrN_2O_3$ | 49.9 | 3.9 | 8.3 | 49.4 | 4.0 | 8.8 |
| 32 | Me | *p*-$NO_2C_6H_4$ | 55 | 194 | $C_{14}H_{13}N_3O_5$ | 55.5 | 4.3 | 13.9 | 55.8 | 4.5 | 14.1 |
| 33 | Ph | *p*-$MeC_6H_4$ | 83 | 171 | $C_{20}H_{18}N_2O_3$ | 71.9 | 5.4 | 8.3 | 71.9 | 5.4 | 8.4 |
| 34 | Ph | *p*-$ClC_6H_4$ | 96 | 145 | $C_{19}H_{15}ClN_2O_3$ | 64.3 | 4.2 | 7.9 | 64.8 | 4.5 | 8.1 |
| 35 | Ph | *p*-$BrC_6H_4$ | 87 | 116 | $C_{19}H_{15}BrN_2O_3$ | 57.1 | 3.8 | 7.0 | 57.6 | 4.8 | 7.2 |
| 36 | Ph | *p*-$IC_6H_4 \cdot H_2O$ | 93 | 132 | $C_{19}H_{15}IN_2O_3$ | 49.2 | 3.7 | 6.1 | 49.2 | 3.3 | 6.4 |

TABLE IV

1-Aryl-3-carbethoxy-5-hydroxymethylpyrazoles (VIII; R = Et) and 3-Carboxy-5-hydroxymethylpyrazole (VIII; R = H)

| Compound No. | R | R′ | Yield % | M.p.° | Formula | Analyses Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 | Et | Ph | 50 | 64 | $C_{13}H_{14}N_2O_3$ | 63.4 | 5.7 | 11.4 | 63.9 | 5.7 | 11.7 |
| 38 | Et | *p*-$MeC_6H_4$ | 52 | 122 | $C_{14}H_{16}N_2O_3$ | 64.6 | 6.2 | 10.8 | 64.8 | 6.4 | 10.7 |
| 39 | Et | *p*-$IC_6H_4$ | 66 | 114 | $C_{13}H_{13}IN_2O_3$ | 41.9 | 3.5 | 7.5 | 41.7 | 3.2 | 7.6 |
| 40 | H | *p*-$BrC_6H_4$ | 68 | 224 | $C_{11}H_9BrN_2O_3$ | 44.4 | 3.2 | 9.5 | 44.7 | 3.4 | 9.2 |

TABLE V

2-Hydroxy-3-(4-phenyl-3- R-Substituted But-3-en-2-onyl)quinoxaline

| Compound No. | R | Yield % | M.p.° | Formula | Analyses Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| 41 | H | 67 | 263 | $C_{18}H_{14}N_2O_2$ | 74.5 | 4.8 | 9.7 | 74.7 | 5.0 | 9.9 |
| 42 | Me | 66 | 239 | $C_{19}H_{16}N_2O_2$ | 75.0 | 5.3 | 9.2 | 75.3 | 5.4 | 9.5 |
| 43 | Ph | 58 | 240 | $C_{24}H_{18}N_2O_2$ | 78.7 | 4.9 | 7.7 | 79.1 | 4.5 | 7.8 |

these 5-styrylpyrazole esters with concentrated hydrochloric acid afforded the corresponding 5-styrylpyrazole-3-carboxylic acids (IV) (see Table II). Ozonolysis of the esters (III) afforded the 3-carbethoxy-5-carbonylpyrazole esters (VI) (see Table III), which were also hydrolyzed to the 5-carbonylpyrazole-3-carboxylic acids (VII) (see Table II). Reduction of the 5-carbonyl groups was carried out with sodium borohydride; 1-*p*-bromophenyl-5-formylpyrazole-3-carboxylic acid (VII) yielded 5-hydroxymethylpyrazole-3-carboxylic acid (VIII; R = H, R′ = *p*-Br-$C_6H_4$) whereas the previously prepared formyl esters (6) (VI, R = H, R′ = aryl) yielded the corresponding ethyl-1-aryl-5-hydroxymethylpyrazole-3-carboxylates (VIII; R = Et, R′ = aryl). Sodium borohydride preferentially attacked the formyl carbonyl leaving the carboxyl and carbethoxyl carbonyl unaffected.

Condensation of 2,4-dioxohexenoates (I; R = H, I; R = Me, I; R = Ph) with *o*-phenylenediamine proceeded

TABLE VI

UV Absorption Data

| Compound No. | λ max (log ε) | | | λ min (log ε) | |
|---|---|---|---|---|---|
| 2 | 224 (4.25) | 277 (4.36) | | 243 (4.04) | |
| 3 | 215 (4.36) | 230 (4.36) | 289 (4.41) | 224 (4.30) | 258 (4.01) |
| 4 | 217 (4.4) | 258 (4.51) | | 231 (4.31) | |
| 5 | 214 (4.16) | 258 (4.25) | | 230 (4.07) | |
| 6 | 222 (4.64) | 258 (4.84) | | 231 (4.53) | |
| 7 | 223 (4.4) | 270 (4.52) | | 233 (4.37) | |
| 8 | 215 (4.47) | 233 (4.51) | 295 (4.27) | 223 (4.38) | 260 (4.25) |
| 9 | 215 (4.46) | 232 (4.51) | 295 (4.27) | 224 (4.40) | 268 (4.26) |
| 10 | 217 (4.52) | 232 (sh) | 285 (4.26) | 265 (4.25) | |
| 29 | 221 (4.32) | 275 (4.83) | | 265 (3.81) | |
| 30 | 226 (4.34) | 268 (3.93) | | 262 (3.91) | |
| 31 | 236 (4.43) | 266 (4.21) | | 263 (4.20) | |
| 32 | 215 (3.79) | 285 (3.44) | | 257 (3.39) | |
| 33 | 214 (4.21) | 255 (4.05) | | 222 (3.88) | |
| 34 | 222 (4.05) | 258 (4.11) | | 235 (3.94) | |
| 35 | 214 (4.22) | 259 (4.75) | | 234 (4.12) | |
| 36 | 221 (4.40) | 255 (4.57) | | 227 (4.39) | |
| 37 | 220 (4.50) | 250 (4.65) | | 228 (4.42) | |
| 38 | 217 (4.11) | 255 (4.01) | 227 (3.74) | | |
| 39 | 214 (4.14) | 261 (4.29) | | 228 (4.05) | |

smoothly yielding oxyquinoxalines (V; R = H, V; R = Me; V; R = Ph). Although 2,4-dioxohexenoates may undergo attack at either the 1,2-carbonyls or the 2,4-carbonyls, the procucts were formulated as oxyquinozalines (V) for two reasons: (a) 2,3-dioxo acids such as dehydroascrobic acid, which are capable of undergoing nucleophilic attack by *o*-phenylenediamine on either the 1,2- or 2,3-carbonyl groups and give six-membered quinoxalines in both cases, cyclize exclusively by 1,2- attack involving the 1-carboxycarbonyl and the C-2 carbonyl group (7,8); (b) Attack on the 2,4- positions of 2,4-dioxohexenoates would afford a less favored seven-membered heterocycle.

The transformation presented here clearly demonstrates that 2,4-dioxohexenoates are useful starting materials for the synthesis of a variety of 5-substituted pyrazoles and 3-substituted 2-oxyquinoxalines in high yields. We are presently studying in more detail the synthetic possibilities of the latter heterocycles.

The uv absorption spectra (see Table VI) of ethyl 5-substituted pyrazole-3-carboxylates show a bathochromic shift due to increased conjugation from 5-hydroxymethyl-pyrazoles (compounds 37-39) which absorb between 250 to 261 nm to the 5-carbonyl derivatives (29-36) which absorb between 255 to 275 nm and finally the 5-styryl derivatives (2-10) which absorb between 258-295 nm. The spectra of all the compounds studied showed no change when measured in non-polar solvents such as cyclohexane or in polar ethanol. This, together with their high extinction coefficient suggests that they are due to $\pi \rightarrow \pi^*$ transition. The weaker $n \rightarrow \pi^*$ transitions usually possess a wavy appearance in non-polar solvents which become blurred in polar solvent and are unaffected by conjugation. Due to the high degree of conjugations in the pyrazoles, the $\pi \rightarrow \pi^*$ transitions are shifted to longer wavelengths and probably overlap the weaker $n \rightarrow \pi^*$ transition (9).

## EXPERIMENTAL

Melting points were measured on a Kofler Block and are uncorrected. Ir spectra were recorded with a Unicam SP200 and uv spectra with a Unicam SP800 instrument in ethanol and in cyclohexane.

5-Styrylpyrazole-3-carboxylates (III).

These compounds were obtained when ethyl 2,4-dioxo-6-phenylhex-5-enoate (I; R = H) or 2,4-dioxo-5-methyl-6-phenylhex-5-enoate (I; R = Me) or 2,4-dioxo-5,6-diphenylhex-5-enoate (I; R = Ph) (0.1 mole) in ethanol was heated under reflux with 0.1 mole of the hydrazine or with the appropriate arylhydrazine hydrochloride (0.1 mole) and sodium acetate (0.1 mole) in ethanol for a period of 2-3 hours. The mixture was then concentrated and cooled and the precipitated product filtered and crystallized from dilute ethanol (see Table I).

5-Styrylpyrazole-3-carboxylic Acids (IV), and 5-Carbonylpyrazole-3-carboxylic Acids (VII).

The esters (III and VI) (1 g.) in concentrated hydrochloric acid (30 ml.) were heated under reflux for the times shown in Table II, and the pyrazole 3-carboxylic acids, which separated from the cooled solution in more than 90% yield, were recrystallized from dilute ethanol.

Ozonolysis of the Esters.

Ice-cold chloroform solutions of the esters (III) (3 g.) were treated with ozonized oxygen for 30 to 60 minutes. After removal of the solvent, the ozonides were decomposed with water and steam distilled until benzaldehyde ceased to pass over. The non-volatile residues were extracted with ether, washed with sodium hydrogen carbonate solution, and dried. Upon evaporation of the ether, the 5-carbonylpyrazole esters (VI) were obtained in crystalline form and recrystallized from dilute ethanol (see Table III).

Borohydride Reduction.

Reduction of formyl esters (6) (VI; R = H) or acids (VII) (0.1 g.) with sodium borohydride (0.02 g.) in 50 ml. water-ethanol (1:1) at room temperature afforded, after extraction with ether and evaporation of the latter, the hydroxymethyl derivatives (VIII; R = Et) and (VII; R = H), respectively, which were crystallized from dilute ethanol (see Table IV).

Oxyquinoxalines (V).

Condensation of the 2,4-dioxohexenoates (II) (5 g.) with *o*-phenylenediamine (3 g.) was achieved by 5 hours refluxing in ethanol (50 ml.). The product obtained after concentration was filtered and recrystallized from dilute ethanol (see Table V).

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