RING TRANSFORMATIONS OF OXAZOLES. NOVEL REARRANGEMENTS OF ETHYL 5-ETHOXY-β-OXO-2-PHENYL-4-OXAZOLEPROPIONATE TO 4-BENZOYLAMINO-PYRAZOLES AND 5-BENZOYLAMINOPYRIMIDINES

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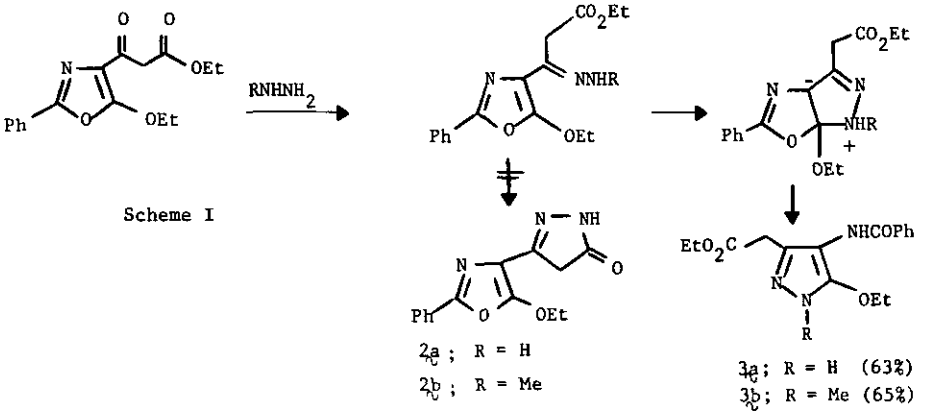
Abstract - Reaction of ethyl 5-ethoxy-β-oxo-2-phenyl-4-oxazolepropionate (1) with hydrazines or guanidines provides the 4-benzoylaminopyrazoles 3a and b or the 2-amino-5-benzoylaminopyrimidines 5a and b respectively.

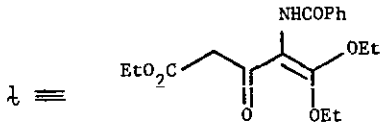
Oxazoles are unusually versatile intermediates in heterocyclic synthesis. Ring transformations of oxazoles have led to at least twenty two different types of heterocyclic systems.[1] In our studies on the Cornforth rearrangement of oxazoles[2] we prepared ethyl 5-ethoxy-β-oxo-2-phenyl-4-oxazolepropionate[3] in 82% yield by the reaction of 2-phenyl-5-ethoxyoxazole-4-carboxylic acid chloride[4] with lithio ethyl trimethylsilylmalonate followed by aqueous hydrolysis of the resulting trimethylsilyl ester and decarboxylation of the keto acid thus formed.[5] This compound undergoes a facile Cornforth rearrangement to yield ethyl (2-phenyl-4-carboethoxyoxazol-4-yl)-acetate.[6] Attempts to prepare the 2-pyrazolin-5-ones 2a or 2b by the reaction of the keto-ester 1 with hydrazine or methylhydrazine in refluxing ethanol (8 h) affords instead ethyl 4-benzamido-5(3)-ethoxy-3(5)pyrazoleacetate (3a)[7] or ethyl 4-benzamido-1-methyl-5-ethoxy-3-pyrazoleacetate (3b)[7] respectively (Scheme I). This is the first example of an oxazole to pyrazole interconversion.



Scheme I

One possible mechanism for this transformation is outlined in Scheme I. The formation of pyrazoles from hydrazine and 3-benzoylfurans[8], 3-acetylpyrroles[9], and 3-acylindoles[10] appears to follow a similar pathway. Likewise the conversion of 2,5-dimethyl-4-acetyloxazole to 2,4-dimethyl-3-acetylamino-4-cyano-5-dicyanomethylpyridine by the reaction of the oxazole with two equivalents of malononitrile in the presence of two equivalents of base is postulated to proceed via this type of mechanism.[11] In the reaction of 1 with methylhydrazine the question of regiochemistry arises, i.e., which pyrazole nitrogen possesses the methyl substituent. Only one regioisomeric product could be isolated in this process and the structure is tentatively assigned as 3b. An x-ray crystallographic structure determination of this compound will be reported in due course.

Recently oxazoles have been used as synthetic equivalents of α-amino ketones.[12] The oxazole 1 may be viewed as a synthetic equivalent of the ketene acetal 4 in its reactions with hydrazines to give the 4-benzoylaminopyrazoles 3a and 3b.



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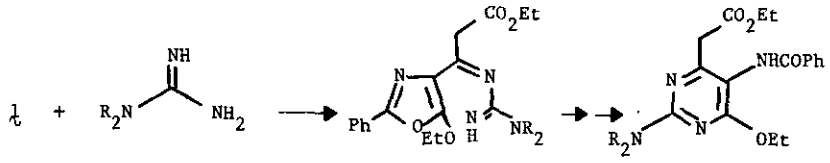
The species 4 or its equivalent 1 should be useful as precursors to other amino heterocycles when combined with various binucleophiles. Thus we obtained ethyl 2-amino-5-benzamido-6-ethoxy-4-pyrimidineacetate (5a)[13] and ethyl 5-benzamido-2-dimethylamino-6-ethoxy-4-pyrimidineacetate (5b)[13] from 1 and guanidine or 1,1-dimethylguanidine respectively (Scheme II). The mechanism of this transformation is presumably analogous to that suggested for pyrazole formation from 1.



Scheme II

5a; R = H (45%)
5b; R = Me (43%)

We are continuing to investigate the scope of these novel oxazole ring transformations.[14,15]

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3. 1; 82% from cyclohexane; mp 66-68°C; m/e 303 (M^+); nmr ($CDCl_3$) δ 1.28 (t, $OCH_2\underline{CH_3}$), 1.53 (t, $OCH_2\underline{CH_3}$), 3.92 (s, $\underline{CH_2}CO_2Et$), 4.23 (q, $O\underline{CH_2}CH_3$), 4.67 (q, $O\underline{CH_2}CH_3$), 7.43 and 7.97 (m, phenyl protons); ^{13}C ($CDCl_3$) ppm, 14.51, 15.24, 46.92, 61.40, 70.53, 116.14, 126.20, 126.69, 129.15; 130.85, 150.80, 160.82, 168.15, 185.74; ir (cm^{-1}, KBr) 1576s, 1595s, 1663s, 1737s, 2975m.
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7. 3a; 63% from cyclohexane/ethyl acetate; mp 166-168°C; m/e 317 (M^+); nmr (DMSO-d_6) δ 1.10, 1.28 (overlapping t, $OCH_2\underline{CH_3}$), 3.62 (s, $\underline{CH_2}CO_2Et$), 4.07, 4.13 (overlapping q, $O\underline{CH_2}CH_3$), 7.53, 7.94 (m, phenyl protons), 9.40 (s, NHCOPh), 11.97 (broad, pyrazole NH); ^{13}C (DMSO-d_6) ppm, 14.11, 15.10, 31.17, 60.75, 64.06, 102.62, 127.85, 128.47, 131.60, 133.10, 134.37, 157.38, 165.83, 168.96; ir (cm^{-1}, KBr) 1505s, 1643s, 1729s, 2965m, 3040s, broad; 3b, 65% from cyclohexane/ethyl acetate; mp 90-92°C; m/e 331 (M^+); nmr (DMSO-d_6) δ 1.07, 1.27 (overlapping t, $OCH_2\underline{CH_3}$), 3.47 (s, $\underline{CH_2}CO_2Et$), 3.60 (s, $N\underline{CH_3}$), 4.05, 4.27 (overlapping q, $O\underline{CH_2}CH_3$) 7.53, 8.00 (m, phenyl protons) 9.53 (s, NHCOPh); ^{13}C (DMSO-d_6), ppm, 14.06, 15.36, 33.50, 34.17, 60.38, 67.99, 101.35, 127.78, 128.54, 131.70, 134.32, 141.06, 147.89, 166.61, 169.91; ir (cm^{-1}) 1593s, 1642s, 1730s, 2970m, 3230s.
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11. P. B. Ghosh and B. Ternai, J. Org. Chem., 1972, 37, 1047.
12. Y. Hamada and T. Shioiri, Tetrahedron Lett., 1982, 23, 1193.
13. 5a; 45% from cyclohexane/ethyl acetate; mp 158-160°C; m/e 344 (M^+); nmr (DMSO-d_6) δ 1.07, 1.25 overlapping t, $OCH_2\underline{CH_3}$), 3.50 (s, $\underline{CH_2}CO_2Et$), 4.02, 4.32 (overlapping q, $O\underline{CH_2}CH_3$), 6.58 (s, $\underline{NH_2}$), 7.53, 8.00 (m, phenyl protons); ^{13}C, (DMSO-d_6) ppm, 14.11, 14.63, 41.90, 60.48, 61.79, 106.73, 127.84, 128.52, 131.67, 133.51, 161.35, 161.50, 165.85, 165.91, 170.85; ir (cm^{-1}, KBr) 1657s, 1725s, 2970w, 3165m, 3275m, 3455s; 5b; 43% from cyclohexane/ethyl acetate; mp 126-128°C; m/e 372 (M^+); nmr ($CDCl_3$) δ 1.22, 1.32 (overlapping t, $OCH_2\underline{CH_3}$), 3.17 (s, $N(\underline{CH_3})_2$), 3.70 (s, $\underline{CH_2}CO_2Et$), 4.17, 4.40 (overlapping q, $O\underline{CH_2}CH_3$), 7.50 (m, phenyl protons and NH), 7.95 (m,

phenyl protons); ^{13}C ($CDCl_3$) ppm, 14.51, 14.82, 37.34, 41.65, 61.35, 62.54, 106.48, 127.76, 128.95, 132.01, 134.73, 160.42, 160.57, 164.55, 166.67, 171.16; ir (cm^{-1}, KBr) 1593s, 1640s, 1730s, 2970m, 3240s.

14. It appears that the reaction of 4-formyl- and 4-ketooxazoles with hydrazines is a general method for the preparation of 4-aminopyrazole derivatives. We will report further details in a subsequent publication.

15. Satisfactory carbon, hydrogen and nitrogen analyses were obtained for all new compounds.

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