A FACILE SYNTHESIS OF NOVEL 3-(1,2,4-TRIAZOL-5-YL)METHYLENE-2-OXO-1,2,3,4-TETRAHYDROQUINOXALINES AND THEIR RELATED COMPOUNDS

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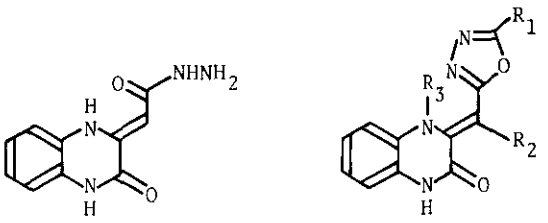
Abstract —— Various new type of triazoles, 3-(1,2,4-triazol-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (4-7) and related compounds (8,9), were synthesized from 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (1).

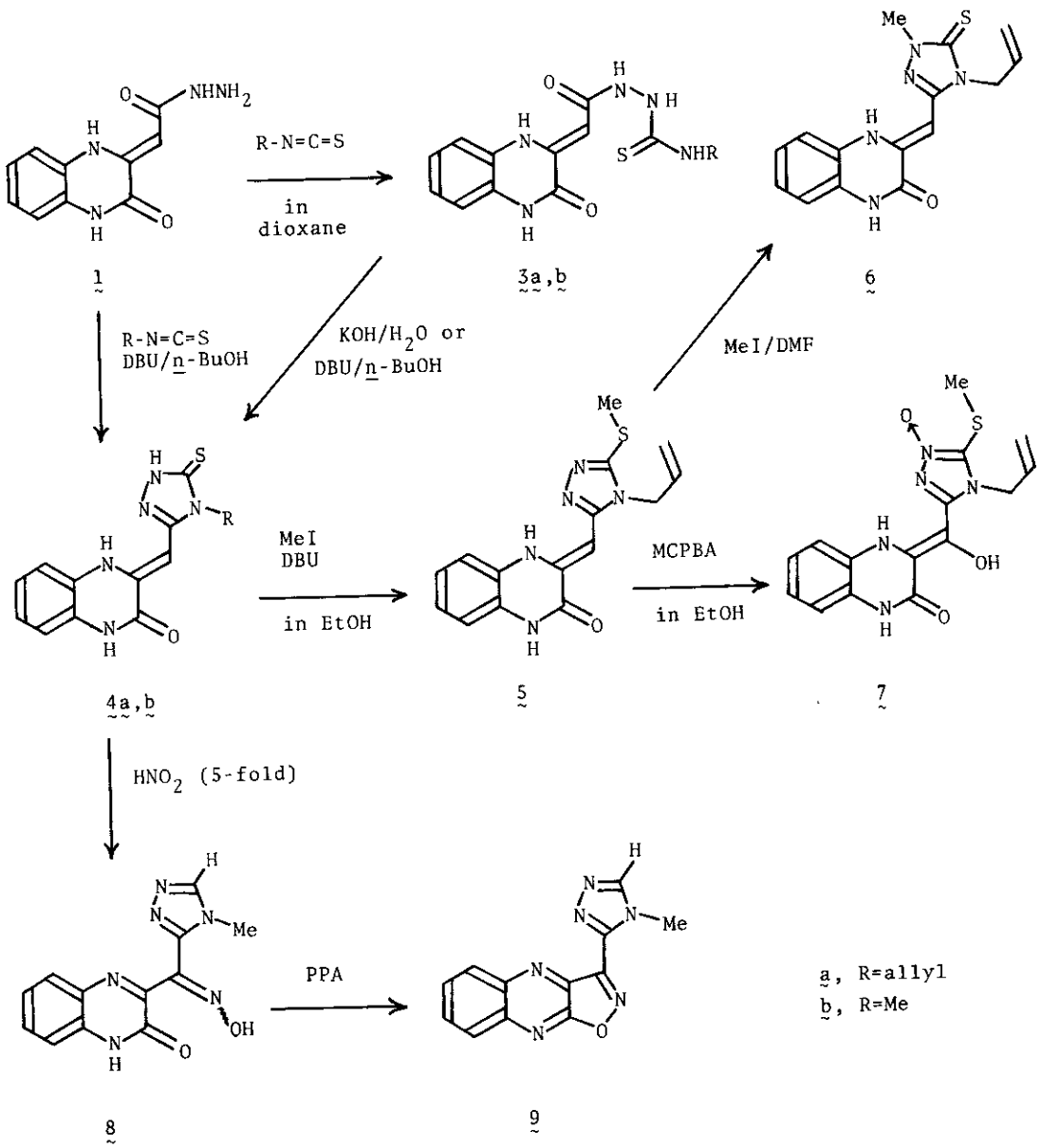
Various 1,3,4-oxadiazoles have been known to possess fungicidal, herbicidal, and bactericidal activities,[1] and we have previously synthesized the new type of 1,3,4-oxadiazoles, 3-(1,3,4-oxadiazol-2-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxalines (2), from 3-hydrazinocarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (1) in order to evaluate the above activities.[1,2] Moreover, many 1,2,4-triazoles have been also reported to possess bactericidal,[3] fungicidal,[4] pesticidal,[5] and plant growth regulatory[6] activities, but there have been few reports concerning the synthesis and biological evaluation of 1,2,4-triazoles having a quinoxalinylmethylene moiety in the 3- or 5-position. This paper describes a convenient synthesis of the above novel type of 1,2,4-triazoles.

The reaction of 1 (10 g, 45.9 mmol) with allyl or methyl isothiocyanate (46.1 mmol) in dioxane (200 ml) afforded the thiosemicarbazide (3a)[7] (13.73 g, 94.4%) or (3b)[8]



1 2

Scheme 1


R-N=C=S
in dioxane
R-N=C=S DBU/n-BuOH
KOH/H2O or DBU/n-BuOH
MeI/DMF
MeI DBU
in EtOH
MCPBA
in EtOH
HNO2 (5-fold)
PPA
1
3a,b
6
4a,b
5
7
8
9
a, R=allyl
b, R=Me

Scheme 2 *

(12.91 g, 96.7%), respectively. Refluxing of 3a or 3b (1 g) with KOH (1.5 eq.) in H_2O (30 ml) effected cyclization[9] to provide 3-(4-allyl-2H-1,2,4-triazoline-3-thion-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4a)[10] (0.76 g, 81%) or 3-(4-methyl-2H-1,2,4-triazoline-3-thion-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (4b)[11] (0.28 g, 29.9%), respectively. Refluxing of 3a or 3b (10 g) in 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) (2 ml) and n-BuOH (400 ml) also afforded 4a (8.02 g, 85.5%) or 4b (8.74 g, 93.2%), respectively, in improved yields. In addition, the reaction of 1 (5 g, 22.9 mmol) with allyl or methyl isothiocyanate (equimolar amount) in DBU (1 ml) and n-BuOH (200 ml) directly produced 4a (4.74 g, 69.1%) or 4b (5.1 g, 81.5%), respectively.

Methylation of 4a (4.22 g, 16.7 mmol) with MeI (2.61 g, 18.4 mmol) in DBU (2.80 g, 18.4 mmol) and EtOH (250 ml) provided 3-(4-allyl-3-methylthio-s-triazol-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (5)[12] (3.37 g, 76.2%). Further refluxing of 5 (2 g, 6.39 mmol) with MeI (1.5 eq.) in DMF (50 ml) induced N_2,-methylation[13] to result in the formation of 3-(4-allyl-2-methyl-1,2,4-triazoline-3-thion-5-yl)methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (6)[14] (0.91 g, 45.5%). Moreover, the reaction of 5 (5 g, 16.0 mmol) with m-chloroperbenzoic acid (MCPBA) (2 eq.) in EtOH (200 ml) caused methylenic C-hydroxylation[15] and N-oxidation to furnish 3-[1-(4-allyl-3-methylthio-s-triazol-5-yl)-1-hydroxy]methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline 2'-oxide (7)[16] (940 mg, 18%), but the allyl group was not epoxidized. The N_2,-oxide assignment was based on the following mass and NMR spectral data. The fragmentary [M^+-16 (O)] ion peak was observed together with the [M^+-17 (OH)] ion peak, which was presumably due to the presence of the SMe group.[17] The methyl and allylic proton signals of 7 appeared in a lower magnetic field than those of 5.

The reaction of 4b (5 g, 18.3 mmol) with $NaNO_2$ (3.79 g, 54.9 mmol) in H_2O (100 ml) and AcOH (200 ml) effected hydroxyimination[18] and sulfur extrusion to afford 3-[1-hydroxyimino-1-(4-methyl-s-triazol-5-yl)]methylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (8)[19] (3.25 g, 65.7%). Heating of 8 (5 g) in polyphosphoric acid (PPA) [H_3PO_4 (20 ml), P_2O_5 (10 g)] produced 3-(4-methyl-s-triazol-5-yl)isoxazolo[4,5-b]quinoxaline (9)[20] (1.86 g, 39.8%).

REFERENCES AND FOOTNOTES

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2. Y. Kurasawa, Y. Moritaki, and A. Takada, Synthesis, 1983, 238.
3. G. Mazzone, F. Bonina, and G. Blandino, Farmaco. Ed. Sci. (Ital.), 1981, 36, 1004 (C. A., 96, 122698m).
4. Eur. Pat. Appl. EP 40345 (C. A., 96, 104256m); Brit. UK Pat. Appl. GB 2075004 (C. A., 96, 104257n); Brit. UK Pat. Appl., GB 2075005 (C. A., 96, 104258p).
5. Ger. Offen. DE 3020500 (C. A., 96, 142863q).
6. Eur. Pat. Appl. EP 44407 (C. A., 96, 199710s).
7. 3a: colorless powder, mp 230-232 °C. ν(KBr): 3300, 1690, 1640 cm^{-1}. δ(DMSO-d_6): 12.43 (s), 11.43 (s), 10.13 (s), 9.63 (s), 9.40 (s), and 9.15 (s) (4H, NH),[21] 8.10 (t, J=4.5 Hz, 1H, CSNHCH$_2$CH=CH$_2$), 8.00-6.70 (m, 4H, aromatic), 5.83 (m, 1H, -CH$_2$-CH=CH$_2$), 5.68 (s, C$_3$=CH-),[21] 5.30-4.87 (m, 2H, -CH$_2$-CH=CH$_2$), 4.10 (m, 2H, -CH$_2$-CH=CH$_2$), 3.72 (s, C$_3$-CH$_2$-).[21]
8. 3b: colorless powder, mp 256-258 °C. ν(KBr): 3300, 3160, 3010, 1670, 1630 cm^{-1}. δ(DMSO-d_6): 11.50 (s), 10.00 (br.s), 9.33 (s), and 9.10 (s) (4H, NH),[21] 7.90 (q, J=4.5 Hz, 1H, CSNHMe), 7.83-6.67 (m, 4H, aromatic), 5.68 (s, C$_3$=CH-),[21] 3.73 (s, C$_3$-CH$_2$-),[21] 2.94 (d, J=4.5 Hz) and 2.88 (d, J=4.5 Hz) (3H, CSNHMe).[21] The Me proton signals became two lines on addition of D_2O.
9. J. H. Wikel and C. J. Paget, J. Org. Chem., 1974, 39, 3506.
10. 4a: yellow powder, mp 334-336 °C. ν(KBr): 3120, 3060, 3010, 1680, 1640, 1610 cm^{-1}. δ(DMSO-d_6): 13.81 (s), 13.57 (s), 12.40 (s), and 11.46 (s) (2H, N_1- and N_4-H),[21] 10.03 (s, 1H, N_2,-H), 7.77-6.67 (m, 4H, aromatic), 5.88 (s, C$_3$=CH-),[21] 5.86 (m, 1H, -CH$_2$-CH=CH$_2$), 5.30-4.83 (m, 2H, -CH$_2$-CH=CH$_2$), 4.68 (dd, J=4.5 Hz, 2H, -CH$_2$-CH=CH$_2$), 4.18 (s, C$_3$-CH$_2$-).[21]
11. 4b: yellow powder, mp above 340 °C. ν(KBr): 3120, 3060, 3010, 1680, 1640, 1610 cm^{-1}. δ(DMSO-d_6): 13.78 (s), 13.47 (s), 12.40 (s), and 11.43 (s) (2H, N_1- and N_4-H),[21] 10.00 (s, 1H, N_2,-H), 7.77-6.77 (m, 4H, aromatic), 5.93 (s, C$_3$=CH-),[21] 4.27 (s, C$_3$-CH$_2$-),[21] 3.50 (s) and 3.53 (s) (3H, N_4,-Me).[21]
12. 5: yellow needles, mp 213-214 °C. ν(KBr): 1675, 1635, 1615 cm^{-1}. δ(DMSO-d_6): 11.33 (s) and 11.13 (s) (2H, N_1- and N_4-H),[21] 7.23-6.73 (m, 4H, aromatic), 5.97 (s, C$_3$=CH-),[21] 5.92 (m, 1H, -CH$_2$-CH=CH$_2$), 5.30-4.53 (m, 4H, -CH$_2$=CH=CH$_2$), 4.23 (s, C$_3$-CH$_2$-),[21] 2.63 (s) and 2.58 (s) (3H, SMe).[21]

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14. 6: yellow needles, mp 285-287 °C. ν(KBr): 1680, 1640, 1610 cm^{-1}. δ(DMSO-d_6): 12.37 (s), 11.40 (s), and 10.08 (s) (2H, N_1- and N_4-H),[21] 7.60-6.70 (m, 4H, aromatic), 5.90 (m, 1H, $-CH_2-CH=CH_2$), 5.87 (s, $C_3=CH-$),[21] 5.27-4.57 (m, 4H, $-CH_2-CH=CH_2$), 4.18 (s, C_3-CH_2-),[21] 3.79 (s) and 3.76 (s) (3H, N_2,-Me).[21]

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16. 7: yellow needles, mp 229-231 °C. ν(KBr): 3220, 1650, 1610 cm^{-1}. δ(DMSO-d_6): 12.03 (s, 1H, N_1-H), 11.22 (s, 1H, N_4-H), 9.85 (s, 1H, OH), 7.30-6.53 (m, 4H, aromatic), 6.00 (m, 1H, $-CH_2-CH=CH_2$), 5.40-4.92 (m, 4H, $-CH_2-CH=CH_2$), 3.20 (s, 3H, SMe).

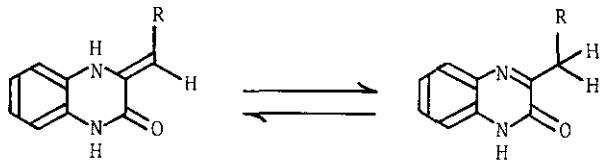
17. R. Grigg and B. G. Odell, J. Chem. Soc. (B), 1966, 218.

18. D. D. Chapman, J. Org. Chem., 1972, 37, 2498; G. W. Danswan, P. W. Hairsine, D. A. Rowlands, J. B. Taylor, and R. Westwood, J. Chem. Soc. Perkin I, 1982, 1049.

19. 8: colorless needles, mp 295-297 °C. ν(KBr): 3140, 1690, 1610 cm^{-1}. δ(DMSO-d_6): 12.53 (s) and 12.18 (s) (2H, N_1-H and OH), 8.57 (s, 1H, C_3,-H), 7.90-7.20 (m, 4H, aromatic), 3.87 (s, 3H, Me).

20. 9: yellow needles, mp 303-305 °C. ν(KBr): 1590, 1555, 1515, 1500 cm^{-1}. δ(DMSO-d_6): 9.91 (s, 1H, C_3,-H), 8.70-8.00 (m, 4H, aromatic), 4.62 (s, 3H, Me).

21. R. Mondelli and L. Merlini, Tetrahedron, 1966, 22, 3253; Y. Kurasawa and A. Takada, Heterocycles, 1983, 20, 1917. The NMR spectra of 1,[2] 2,[2] 3-7 in DMSO-d_6 exhibit the following tautomers A and B, and hence the extra NH and C_3-CH_2- protons peaks are observed.



A B

* Satisfactory mass spectral and microanalytical data were obtained for all new samples.

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