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THE SYNTHESIS OF FUSED TRIAZOLO-OXADIAZOLES[1]

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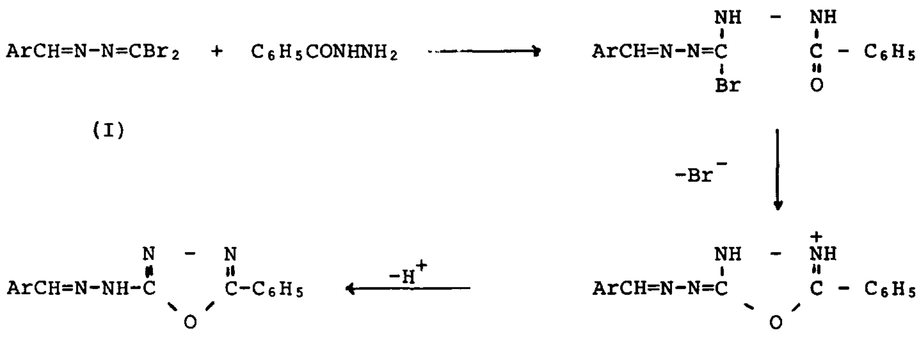
The oxidation of heterocyclic aldehydic hydrazones with either bromine or lead tetra-acetate leads to a variety of fused triazole systems, e.g. triazolotetrazoles,[2a] triazolotriazoles[2b] and triazolothiazoles.[2c] We now report several routes to a new fused ring-system, triazolo-oxadiazoles - a system whose existence has been suggested previously but not further authenticated.[3]

We used as substrates in our first approach the oxadiazolyl-hydrazones (II). These we prepared either by the five-step procedure we have outlined earlier[4] or by the following novel reaction (Scheme 1) involving reaction of substituted dibromo-diazabutadienes (I) with benzhydrazide and triethylamine in refluxing benzene for 12 hours, when compounds (II) were formed in very good (ca. 80%) yields.

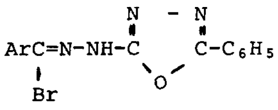


(I)

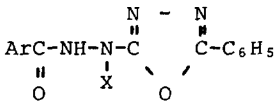
(II)

Scheme 1

When we attempted bromination of the hydrazones (II, ≡ Hy) under our usual conditions[2] (1 mole hydrazone and 2 moles of bromine in glacial acetic acid with stirring for 24 hours at room temperature) unexpectedly[5] the products were the hydrazone perbromides ($Hy.HBr_3$)[6] in 85-90% yields. These materials liberated iodine from acidified potassium iodide solution. They brominated acetanilide in acetic acid solution and when distributed between sodium thiosulphate solution and ether they regenerated the parent hydrazones quantitatively. We had previously regarded the formation of such perbromides as a serious obstacle in the synthesis of hydrazidic halides (such as III) but with these particular compounds, due to favourable solubility factors, we were able to overcome this obstacle for the first time. Treatment of hydrazones (II) with 1.1 equivalents of bromine in the presence of two equivalents of sodium acetate in acetic acid suspension at room temperature for two hours yielded the oxadiazolyl hydrazidic bromides (III) in excellent (80-90%) yields, together with small (2-3%) quantities of the N-acetyl-hydrazides (IVA). These hydrazidic bromides when refluxed with 2.5 equivalents of triethylamine in benzene solution for 8 hours yielded

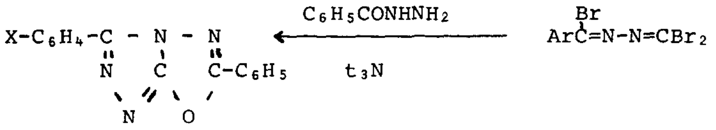


(III)



IV, A, X=Ac

IV, B, X=H



(V) (VI)

the s-triazolo{3,4-b}-1,3,4-oxadiazoles (V) in quantitative (> 95%) yields. (m.p. of products are p-NO_2 : m.p. 267-8°; p-Br, m.p. 218-19°; p-Cl, 213-14°; m-Br, m.p. 185-7°; H, m.p. 179-180°). Interestingly when the hydrazones (II) were treated with lead tetra-acetate in acetic acid for 3 hours at room temperature, only t.l.c. evidence for the formation of compounds (V) were obtained. Instead large quantities of gums and 40-50% yields of the N-acetyl hydrazides (IVA) were obtained.

The second general method involved merging several of the steps detailed above. In this procedure tribromo-diazabutadienes (VI) were refluxed with one equivalent of benzhydrazide and three equivalents of triethylamine in benzene solution for 8 hours when the bicyclic compounds (V) were formed in 75-80% yields. Clearly the hydrazidic bromides (III) are involved as intermediates. {In a trial experiment using one equivalent of the p-nitrophenyl compound (VI, Ar=p-$NO_2C_6H_4$) with three equivalents of benzhydrazide as both base and reagent in benzene solution at room temperature for one hour 32% of the corresponding hydrazidic bromide (III, Ar=p-$NO_2C_6H_4$) was isolated amongst a variety of other products}. Incidentally refluxing compounds (III) in 50% aqueous acetone for short periods (*ca.* 30 minutes) afforded good (*ca.* 60%) yields of the bicyclic compounds (V) and 30-40% yields of the corresponding hydrazides (IVB).

The bicyclic compounds were labile and for example when refluxed briefly (3-5 minutes) in glacial acetic acid smoothly opened to yield the substituted 4-aminotriazolones (VII) in good (> 80% yields) {m.p. of representative compounds of this class (p-X=NO_2, 320°; Br, $263\text{-}64^{\circ}$; Cl, 260°)]. Similarly the oxadiazolyl ring in compounds (V) was cleaved either by refluxing (for 45 minutes) in 0.1N HCl or in 0.05N NaOH, in 50% aqueous dioxane solutions.[7] In effect the sequence (III) ———→ V ———→ (VII) involves heterocyclic ring interconversion, an oxadiazole ring becoming a triazole ring. This is a known process in triazole chemistry and the greater stability of the triazole ring systems[8] explains why compounds (V) ring-open at the oxadiazolyl function. This in turn may explain the difficulties of previous workers in attempting synthesis of the fused oxadiazolyl triazole ring system (V).

(V) (VII)

References

[1] This paper is Part VI of the series on halogeno-diazabutadienes. Parts 1 to V, F.L. Scott and D.A. Cronin, Chemistry and Industry, 1757 (1964); F.L. Scott, J.A. Cronin and J. Donovan, Tetrahedron Letters, 4615 (1969); F.L. Scott, J. Donovan and J.K. O'Halloran, Tetrahedron

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[2] (a) R.N. Butler and F.L. Scott, J. Chem. Soc. (C), 1711 (1968); (b) F.L. Scott and T.A.F. O'Mahony, Tetrahedron Letters, 1841 (1970); (c) R.N. Butler, P.A. O'Sullivan and F.L. Scott, J. Chem. Soc. (C), in press.

[3] K.T. Potts, Chem. Rev., 61, 87 (1961) has reported the isolation of one compound possessing this triazolo-oxadiazolyl ring system. However, in his subsequent paper, K.T. Potts, J. Org. Chem., 28, 543 (1963), this claim was not repeated. Our evidence suggests that perhaps the compound isolated in Potts' earlier work was not a fused ring material but instead an open-chain benzoyl aminotriazole.

[4] R.N. Butler, T. Lambe and F.L. Scott, Chemistry and Industry, 628 (1970).

[5] Bromination of the analogous p-substituted arylidene-5-(3-phenyl)-1,2,4-triazolyl hydrazones does not involve perbromides but yields hydrazidic halides, F.L. Scott and J.B. Aylward, Tetrahedron Letters, 841 (1965).

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[8] H. Gehlen, Liebigs Ann. Chem., 563, 185 (1949).

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