SYNTHESIS OF 1,2,4-TRIAZOLO FUSED HETEROCYCLES

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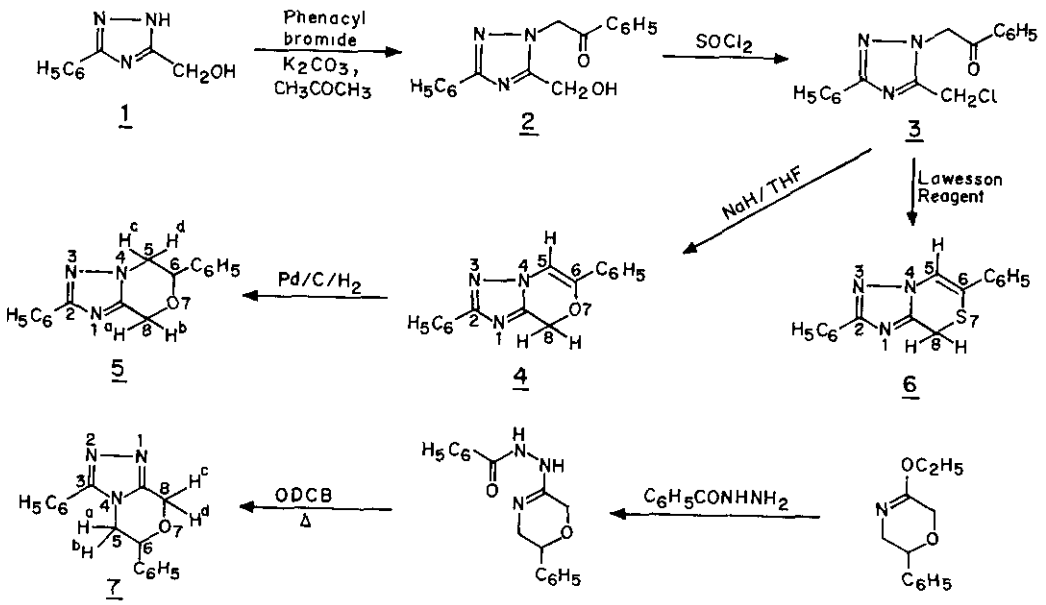
Abstract - Synthesis of bicyclic and tetracyclic ring systems containing 1,2,4-triazole unit has been achieved by alkylation of substituted 1,2,4-triazoles followed by base catalysed cyclocondensation.

The broad spectrum of activity[1,2,3] associated with substituted 1,2,4-triazoles prompted us to carry out the synthesis of novel fused ring systems containing the 1,2,4-triazole unit. Only recently the 8-oxo analogue of the 1,2,4-triazolo[5,1-c][1,4]oxazine system has been reported[4].

Herein, we describe a synthesis of triazolo fused bicyclic and tetracyclic systems by base catalysed cyclocondensation of the substituted 1,2,4-triazole derivatives.

On the basis of our earlier study[5] in the regiochemistry of alkylation in substituted 1,2,4-triazoles, it is now possible to predict the major regioisomer formed on alkylation. 3-Hydroxymethyl-5-phenyl-1,2,4-triazole 1[6] was phenacylated with phenacyl bromide and anhydrous potassium carbonate in acetone to give 2 (94%, mp 175-193°C)[7]. Structure 2 was assigned to the major product, the validity of which was verified by subsequent transformations. Compound 2 on treatment with thionyl chloride in chloroform yielded 3 (99%, mp 143°C). Reaction of 3 with sodium hydride in tetrahydrofuran gave a crude product which on column chromatographic separation over silica gel furnished 2,6-diphenyl-8H-[1,2,4]triazolo[5,1-c][1,4]oxazine 4 (55%, mp 154°C) (Scheme I). The structure of 4 was confirmed by pmr (Table 1), mass spectrum and elemental analysis. Further, 4 on catalytic hydrogenation over palladised charcoal gave 5 (94%, mp 111-112°C). Pmr (Table 1), mass spectrum and elemental analysis confirmed the structure of 5. In the uv, 4 showed maxima at 310 nm and 205 nm whereas 5 gave peaks at 240 nm and 200 nm.

It is well established in the literature[8,9,10], that alkylation in substituted 1,2,4-triazoles occurs mainly at vicinal nitrogens rather than at N_4 because of their enhanced nucleophilicities and N_4 derivatives are either nor formed at all



SCHEME - 1.

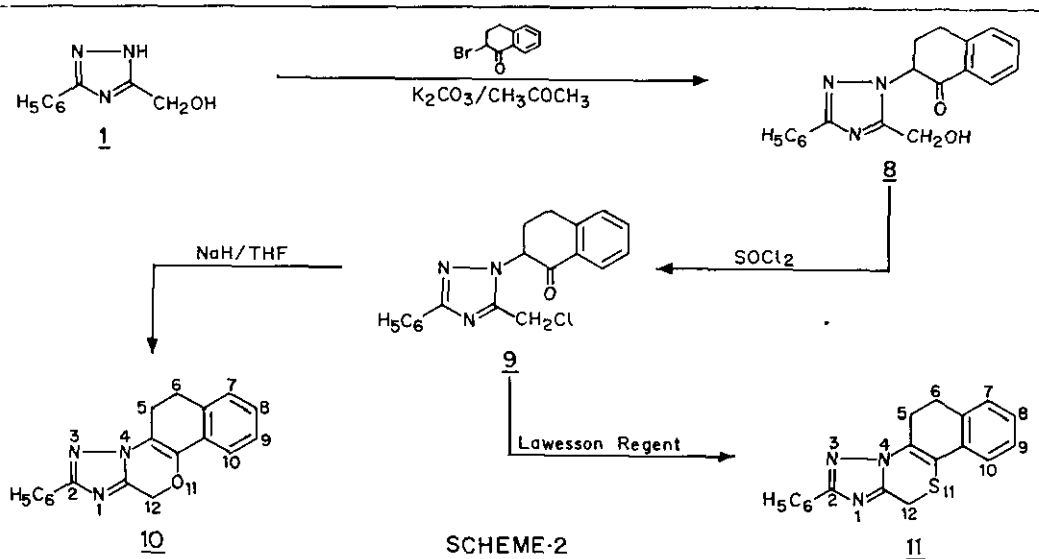
or obtained in very low yields. To rule out the remote possibility of the initial phenacylation having occurred at N_4 to give the isomeric bicyclic compound 3,6-diphenyl-8H-5,6-dihydro[1,2,4]triazolo[3,4-c][1,4]oxazine 7, the latter was synthesised (56%, mp 164°C) unambiguously starting from 3-ethoxy-6-phenyl-3,4-dehydromorpholine[11] (Scheme I). Comparison of spectroscopic data, melting points and tlc behaviour of compounds 5 and 7 showed that they are two different compounds. This confirmed the correct structure assignment to the compounds 2 to 5.

In order to get the thione analogue of 3, it was reacted with Lawesson reagent[12] in refluxing toluene. Instead of the required thione, the cyclized product 2,6-diphenyl-8H-[1,2,4]triazolo[5,1-c][1,4]thiazine 6 (50%, mp 148-149°C) was obtained.

To prepare a tetracyclic derivative containing 1,2,4-triazole, 1 was alkylated with 2-bromo-1-tetralone to give compound 8 (50%, mp 181°C), which was converted to its chloromethyl derivative 9 (99%, mp 183-184°C) with thionyl chloride (Scheme II). Compound 9 on reaction with sodium hydride in tetrahydrofuran gave 2-phenyl-12H-5, 6-dihydronaphtho[1,2-b][1,2,4]triazolo[1,5-d]-[1,4]oxazine 10 (71%, mp 182°C). Similarly, 9 with Lawesson reagent gave 2-phenyl-12H-5,6-dihydronaphtho[1,2-b][1,2,4]triazolo[1,5-d]thiazine 11 (46%, mp 192°C).

TABLE 1

Compound	Mass (m/z)	Pmr ($CDCl_3$) δ ppm
4	275 (M^+), 137.5 (M^{++}) 105 ($C_6H_5CO^+$)	5.5 (s, 2H), 7.3 (s, 1H), 7.4 (m, 8H), 8.1 (dd, J=6 Hz, 2 Hz, 2H).
5	277 (M^+),171(M^+-C_6H_5CHO)	4.2 (dd, J=12 Hz, 4 Hz, 1H)-H^c, 4.5 (dd, J=12 Hz, 11 Hz, 1H)- H^d, 5.0 (dd, J=11 Hz, 4 Hz, 1H)-CHPh, 5.0 (d, J=16 Hz, 1H)-H^a, 5.3 (d, J=16 Hz, 1H)-H^b, 7.4 (s, 8H), 8.1 (dd, J=6 Hz, 2 Hz, 2H).
6	291(M^+), 145.5 (M^{++}), 121 ($C_6H_5CS^+$)	4.3 (s. 2H), 7.3 (m, 8H), 7.5 (s, 1H), 8.0 (dd, J=6 Hz, 2 Hz, 2H).
7	277(M^+), 171(M^+-C_6H_5CHO)	4.1 (m, 2H)-H^a,-H^b, 4.8 (dd, J=9 Hz, 4 Hz, 1H)-CHPh, 5.1 (d, J=16 Hz, 1H)-H^c, 5.4(d, J=16 Hz, 1H)-H^d, 7.4 (m, 8H), 7.7 (dd, J=6 Hz, 2 Hz, 2H).
10	301(M^+)	3.1 (s, 4H), 5.5 (s, 2H), 7.3 (m, 7H), 8.0 (dd, J=6 Hz, 2 Hz, 2H).
11	317 (M^+)	3.1 (m, 4H), 4.2 (s, 2H), 7.4 (m, 7H), 8.0 (dd, J=6 Hz, 2 Hz, 2H).



SCHEME-2

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