

SYNTHESIS OF 1,2,4-TRIAZOLO FUSED HETEROCYCLES

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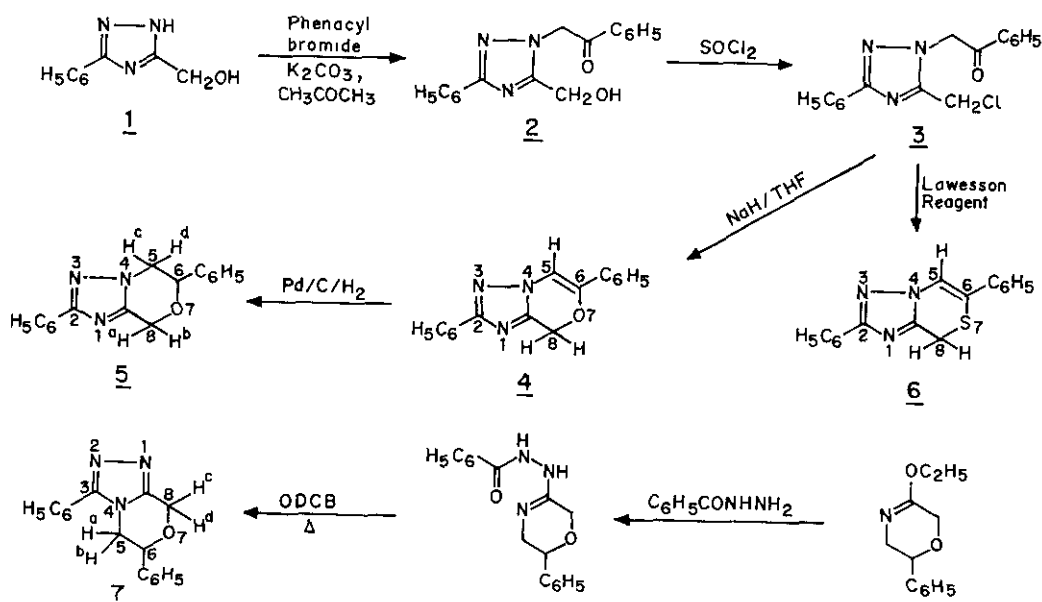
Abstract - Synthesis of bicyclic and tetracyclic ring systems containing 1,2,4-triazole unit has been achieved by alkylation of substituted 1,2,4-triazoles followed by base catalysed cyclocondensation.

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 reported⁴.

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 study⁵ 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 1⁶ 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 N₄ because of their enhanced nucleophilicities and N₄ derivatives are either not formed at all



SCHEME - 1.

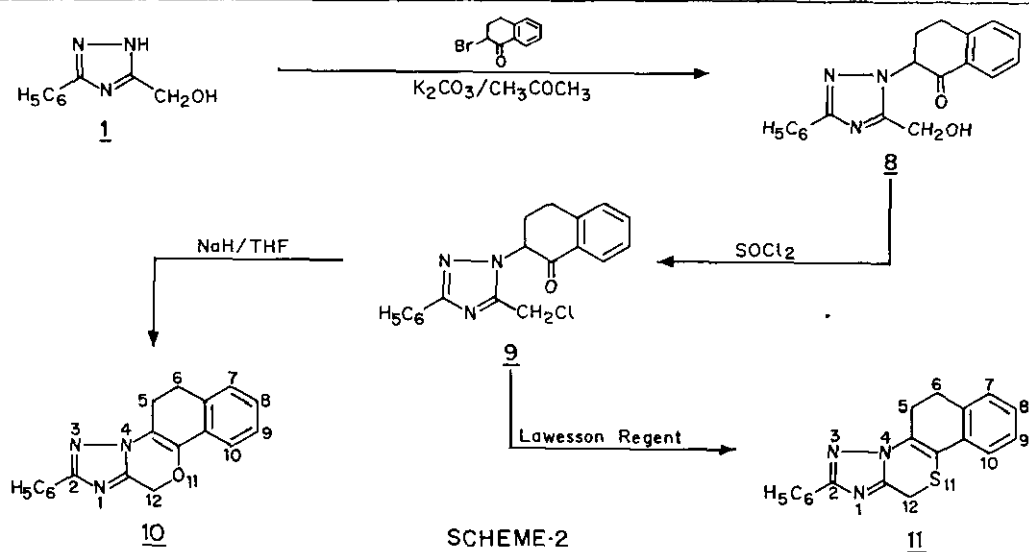
or obtained in very low yields. To rule out the remote possibility of the initial phenacylation having occurred at N_4 to give the isomeric bicyclic compound 3,6-diphenyl-8H-5,6-dihydro[1,2,4]triazolo[3,4-c][1,4]oxazine **7**, the latter was synthesised (56%, mp $164^\circ C$) unambiguously starting from 3-ethoxy-6-phenyl-3,4-dehydromorpholine¹¹ (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 reagent¹² 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 $148-149^\circ C$) 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 $181^\circ C$), which was converted to its chloromethyl derivative **9** (99%, mp $183-184^\circ C$) 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 $182^\circ C$). 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 $192^\circ C$).

TABLE 1

Compound	Mass (m/z)	Pmr (CDCl ₃) δ ppm
4	275 (M ⁺), 137.5 (M ⁺⁺) 105 (C ₆ H ₅ CO ⁺)	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 ₆ H ₅ CHO)	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 ₆ H ₅ CS ⁺)	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 ₆ H ₅ CHO)	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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7. Crystallisation and column chromatography reduced the range in melting point but did not yield a sharp melting compound. However, the crude product shows a clean PMR (CDCl₃): δ 4.9 (s, 2H, -CH₂OH), 5.8 (s, 2H, N-CH₂-CO-), 7.5 (m, 6H, ArH). 8.0 (m, 4H, ArH). The range in melting point is probably due to small quantities of regio isomers. The crude product was therefore used as such.
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