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REACTION BETWEEN 8-CHLOROTHEOPHYLLINE AND EPOXIDES. A SIMPLE PREPARATION OF OXAZOLIDO[2,3-f]PURINES

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Abstract: The reaction of epoxides with 8-chlorotheophylline (1) produced the corresponding oxazolido[2,3-f]purines via nucleophilic addition and intramolecular nucleophilc substitution.

Fused heterocyclic compounds can be obtained from intramolecular cyclization reactions.[1-3] Recently, Hesek et al[1c] established a simple method to prepare pyrimido[2,1-f]purines in which the reactive groups H-N< and Br in 8-bromotheophylline are substituted by the required moieties which readily undergo intramolecular 1,3-dipolar cycloaddition reaction. However, one-pot method from 8-halogenated theophylline to the corresponding fused theophylline was not reported previously. This paper reports a simple preparation of oxazolido[2,3-f]purines from the reaction of 1 with epoxides.

A typical reaction was carried out as follows. 0.858 g (4 mmol) of 8-chlorotheophylline (1), 1.20 g (8 mmol) of phenyl glycidyl ether (2a) and 0.150 g (0.3 mmol) of tetrabutylphosphonium bromide were added to 2.0 ml of diglyme. The mixture was allowed to keep at 90°C for 12 h resulting in a white solid precipitation. After cooling, the precipitated solid was filtered and washed several times by small amount of acetone and dried under vacuum. The yield of the product, 1,3-dimethyl-2,4-dioxo-7-phenoxymethyl-1,2,3,4,6,7-hexahydrooxazolido[2,3-f]purine, was 1.0 g (79.8%). Some products and their spectrum data are summarized in Table I.

The reaction of epoxides with 1 proceeded in the heterogeneous system, because 1 did not dissolve in the solvent. However, with the proceeding of the reaction (in 1 h), a homogeneous solution was formed. When the solution was further heated at 90°C for 3-5 h, much amount of white solid precipitated again. To clarify the pathway of the reaction, the quenching of the homogeneous solution was examined. For example, the half solution, which was formed from the reaction of 1 (4 mmol) in 3.0 ml of epoxide 2b (27 mmol) after 30 min at 90°C, was removed from the reaction flask and quickly cooled in an ice bath, while the residue in the reaction flask was allowed to keep further for 5 h at the same temperature. From the isolated samples, it was identified that the quenched fraction was adduct 3b and the residue one was the fused product 4b. Besides, this reaction also gave 1-chloro-2-hydroxy-3-allyloxypropane.

So, the mechanism of the reaction between epoxides and 1 is assumed as follows. The nucleophilic NH group in 1 attacked on the epoxy ring leading to the adducts 3a-c, and then the intramolecular nucleophilic substitution reaction took place leading to the cyclization products 4a-c. However, the reaction of cyclohexene oxide with 1 produced adduct 3d which did not transform to the oxazolido fused ring. It seems that the hydroxy group in adduct 3d occupied trans position in cyclohexane ring against theophylline moiety so that the intramolecular cyclization reaction was inhibited by the steric strain.

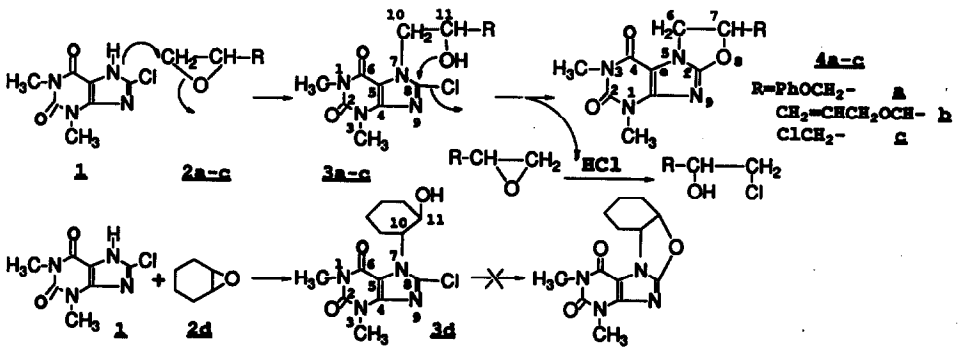

Table I. Products of The Reaction of Epoxides with 8-Chlorotheophylline*

Pro./ Yield(%) / mp(°C) / ^{1}H-NMR (90MHz/$CDCl_3$), δ J(Hz)
4a / 79.8/ 166.7-8.5/ 3.39(s,3H,3-CH_3); 3.57(s,3H,1-CH_3); 4.19-4.5(dd and dd,2H,CH_2OPh, J_1=4.0, J_2=4.2, J_3=J_4=10.9); 4.37-4.7(dd and dd, 2H, H-6, J_1=7.5, J_2=7.9, J_3=J_4=9.9); 5.57-5.84(m,1H, H-7); 6.83-7.4(m, 5H, Ar-H)
4b / 68.1/ 151.5-3.2/ 3.38(s,3H,3-CH_3); 3.52(s,3H,1-CH_3); 3.65-3.97(dd and dd, 2H, 7-CH_2O, J_1=3.7,J_2=4.0, J_3=J_4=11.2); 4.02-4.11(ddd, 2H, O-CH_2CH=C, J_1=1.1, J_2=1.3, J_3=J_4=5.5); 4.23-4.58(dd and dd, 2H,H-6, J_1=7.5,J_2=8.1, J_3=J_4=9.7); 5.14-5.38(m,2H, CH_2=C); 5.42-5.64(m,1H,H-7); 5.72-6.09(m, 1H, CH=CH_2)
4c / 73.7/ 206-208/ 3.39(s, 3H,3-CH_3); 3.52(s, 3H,3-CH_3); 3.81-4.09(dd and dd,2H,CH_2Cl, J_1=4.6, J_2=5.3, J_3=J_4=8.6); 4.29-4.69(dd and dd, 2H,H-6,J_1=6.8, J_2=8.4, J_3=J_4=10.1); 5.51-5.78(m, 1H, H-7)
3b / - / 75.5-6.2/ 2.17(s,1H, HO-11 uncoupled); 3.39(s,3H,1-CH_3); 3.55(s, 3H,3-CH_3) 3.43-3.63(m,2H,H-12); 4.01-4.15(ddd, 2H, H-14,J_1=1.1, J_2=1.3,J_3=J_4=5.5); 4.11-4.34(m,1H,H-11); 4.25-4.63(dd and dd, 2H, H-10, J_1=4.8, J_2=7.0, J_3=J_4=13.3); 5.26-6.14(m, 3H, CH=CH_2)
3d / 72.3/ 177.0-8.9/ 1.15-2.85(br and m, 9H, c-Hex and HO-11); 3.37(s, 3H,1-CH_3); 3.56(s, 3H, 3-CH_3); 4.14- 4.73(br and m, 2H, H-10,H-11)

* isolated yield; IR (KBr, cm^{-1}) for 3b (ν_{OH}=3428) and 3d (ν_{OH}=3492)

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