Tetrahedron Letters No. 13, pp 1187 - 1190, 1974. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 3-(1H-TETRAZOL-5-YL)CHROMONES AND A NOVEL DEGRADATION REACTION OF TETRAZOLE RING WITH VILSMEIER REAGENTS

Akira Nohara

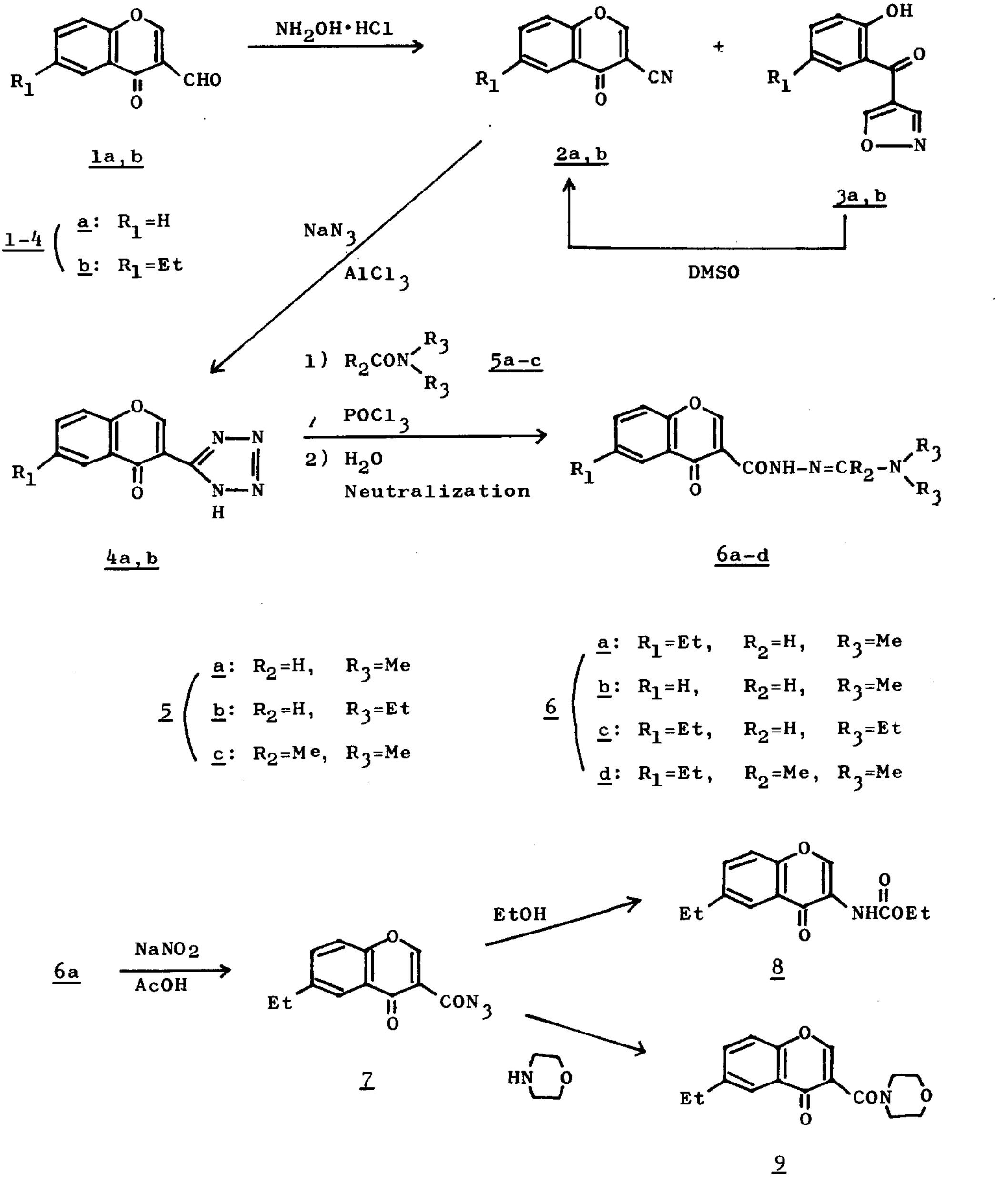
Medicinal Research Laboratories, Central Research Division,
Takeda Chemical Industries, Ltd., Higashiyodogawa, Osaka, Japan

(Received in Japan 9 February 1974; received in UK for publication 19 February 1974)

Chromone-2-carboxylic acids and 2-(1H-tetrazol-5-yl)chromones are currently much interested on account of their antiallergic activities, and several reports have been made on the chemistry and syntheses of them[1]. However there is no report concerning the synthesis and biological activity of 3-(1H-tetrazol-5-yl)chromones. We now wish to report the synthesis of 3-(1H-tetrazol-5-yl)chromones and also a novel degradation reaction of tetrazole ring with Vilsmeier reagents.

The reaction of 4-oxo-4H-1-benzopyran-3-carboxaldehyde 1a[2,3] with hydroxylamine hydrochloride in 95% ethanol under the presence of hydrochloric acid[4] afforded in one step 3-carbonitrile derivative 2a, mp 177-178°, 75.6% yield, together with 4-(2-hydroxybenzoyl)isoxazole 3a, mp 116-117°, 7.7% yield. Similarly, 2b, mp 123-124°, and 3b, mp 38-39° were obtained from 1b[3] in 69% and 5.5% yields, respectively. 3a was converted to 2a in 88% yield by heating in dimethyl sulfoxide.

The general reaction of 2a with sodium azide and ammonium chloride in dimethylformamide[5] did not give the desired 3-(1H-tetrazol-5-yl)chromone 4a because of the decomposition of 2a during the reaction. However, the reaction of 2a with sodium azide in the presence of aluminum chloride in tetrahydrofuran[6], afforded 4a, mp 297-299° (decomp.) in 80% yield. Similarly 4b, mp 223-224°, was obtained from 2b, in 81% yield.



1-4 a: R_1=H
b: R_1=Et

5 a: R_2=H, R_3=Me
b: R_2=H, R_3=Et
c: R_2=Me, R_3=Me

6 a: R_1=Et, R_2=H, R_3=Me
b: R_1=H, R_2=H, R_3=Me
c: R_1=Et, R_2=H, R_3=Et
d: R_1=Et, R_2=Me, R_3=Me

Many reports have been made on the degradation reaction of 5-substituted tetrazoles to heterocyclic compounds by the use of acylating agents[7] or photochemical reaction[8]. Little has been known, however, about the formation of non-heterocyclic compounds except N,N'-dibenzoyl-urea of -hydrazine produced from unsubstituted tetrazole[9].

A novel degradation reaction of 5-substituted tetrazoles which are converted to substituted formamide hydrazone derivatives with Vilsmeier reagents, has been found. Namely, an addition of phosphorus oxychloride (4.0 ml) to the dimethylformamide solution (50 ml) of 6-ethyl-3-(1H-tetrazol-5-yl)chromone 4b (11.2 g) at room temperature caused the immediate evolution of nitrogen gas. Water (500 ml) was added to the solution which was neutralized with sodium hydroxide solution to afford N,N-dimethylformamide N^2-(6-ethylchromone-3)-carbohydrazone 6a, mp 187-188°, 83% yield, ir (KBr)cm^{-1}: 1670 (CONH), 1635 (pyrone CO); nmr (CF_3COOD) δ 9.27 (1H, s, H_2), 8.15 (2H, near s, H_5 and -CH=N-), 7.92 (1H, dd, J=8 and 2Hz, H_7), 7.70 (1H, d, J=8Hz, H_8), 3.53 (3H, s, NMe), 3.40 (3H, s, NMe), 2.97 (2H, q, J=7Hz, CH_2), 1.41 (3H, t, J=7Hz, Me). Similarly, 6b, mp 208-209°, 84% yield, was obtained from 4a.

The analogous reaction of 4b with diethylformamide 5b and phosphorus oxychloride afforded 6c, mp 151-152°, 57% yield. Similarly 6d, mp 137-138°, 56.5% yield, was obtained by the reaction of 4b with dimethylacetamide 5c and phosphorus oxychloride.

6a containing the acyl hydrazide group protected in a type of Schiff base was converted by the reaction with sodium nitrite in acetic acid at room temperature to the acyl azide 7, mp 82-84° (decomp.), 57% yield, ir (KBr)cm^{-1} 2140 (CON_3), 1660 (pyrone CO). 7 was converted to the ethyl carbamate 8, mp 79-81°, 89% yield by heating with ethanol, and also to the amide 9, mp 165-166° by the reaction with morpholine in benzene.

References

1. G. P. Ellis and G. Barker, Progr. Med. Chem., 9, Part I, 65, Butterworths (1972); H. Cairns, C. Fitzmaurice, D. Hunter, P. B. Johnson, J. King, T. B. Lee, G. H. Lord, R. Minshull, and J. S. G. Cox, J. Med. Chem., 15, 583 (1972); G. P. Ellis and D. Shaw, J. Chem. Soc., Perkin I, 1972, 779; Idem, J. Med. Chem., 15, 865 (1972).

2. F. Eiden and H. Haverland, *Arch. Pharm.*, **300**, 806 (1967).
3. A. Nohara, T. Umetani and Y. Sanno, *Tetrahedron Letters*, 1995 (1973).
4. J. A. Findley and C. S. Tang, *Can. J. Chem.*, **45**, 1014 (1967).
5. W. G. Finnegan, R. A. Henry and R. L. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).
6. C. Arnold Jr. and D. N. Thatcher, *J. Org. Chem.*, **34**, 1141 (1969).
7. R. Huisgen, J. Sauer and H. J. Sturm, *Angew. Chem.*, **70**, 272 (1958); Idem, *Chem. Ber.*, **93**, 2106 (1960); R. Huisgen, H. J. Sturm and M. Seidel, Ibid., **94**, 1555 (1961); R. Huisgen, J. Sauer and M. Seidel, *Chem. and Ind.*, 1114 (1958); Idem, *Chem. Ber.*, **93**, 2885 (1960).
8. P. Scheiner, *J. Org. Chem.*, **34**, 199 (1969).
9. G. Heller, *Ber.*, **40**, 114 (1907).