A SIMPLE PREPARATION OF 2-ARYL-4H-3,1-BENZOXAZIN-4-ONES

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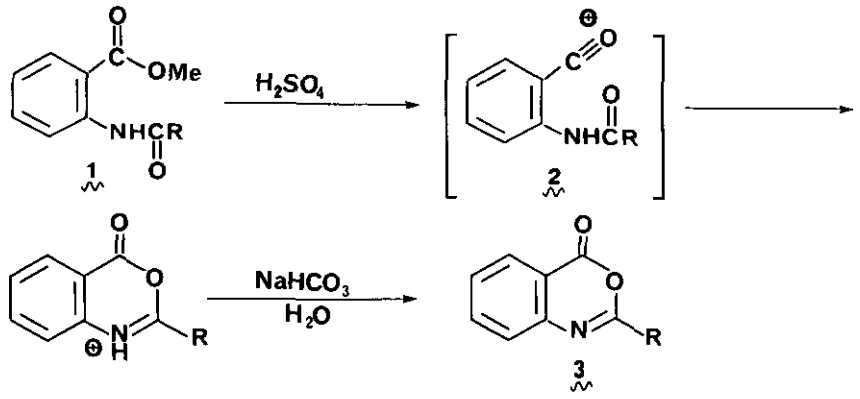
Abstract -- Room temperature treatment of methyl N-acylanthranilates with concentrated sulfuric acid leads to 2-aryl-4H-3,1-benzoxazin-4-ones in excellent yield.

A major method of preparation of 2,3-disubstituted quinazolin-4(3H)-ones, many of which exhibit useful biological activity, consists in the reaction of amines with 2-substituted 4H-3,1-benzoxazin-4-ones (3, R = alkyl, aryl).[1] The latter compounds are generally accessible through either the cyclodehydration of N-acylanthranilic acids by acetic anhydride,[2] or the reaction of anthranilic acid with acid chlorides in pyridine.[3] In a recent investigation, it was found that methyl 2-ureidobenzoates are conveniently converted into N-substituted 2-amino-4H-3,1-benzoxazin-4-ones (3, R = NHalkyl, NHaryl) by the action of concentrated sulfuric acid.[4] Because of the close structural analogy, it was desirable to find out whether this method could also be used for the preparation of 2-alkyl- and 2-aryl-4H-3,1-benzoxazin-4-ones.



a,	R = Ph	f,	R = 4-$CH_3OC_6H_4$	k,	R = 2,6-$Cl_2C_6H_3$
b,	R = 2-$CH_3C_6H_4$	g,	R = 2-ClC_6H_4	l,	R = 3,4-$Cl_2C_6H_3$
c,	R = 3-$CH_3C_6H_4$	h,	R = 3-ClC_6H_4	m,	R = 3-$NO_2C_6H_4$
d,	R = 4-$CH_3C_6H_4$	i,	R = 4-ClC_6H_4	n,	R = 4-$NO_2C_6H_4$
e,	R = 4-n-$C_3H_7C_6H_4$	j,	R = 2,4-$Cl_2C_6H_3$	o,	R = 3,5-$(NO_2)_2C_6H_3$

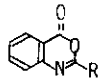
It has now been established that room temperature treatment of methyl N-aroylanthranilates (1, R = aryl) with concentrated sulfuric acid leads to 2-aryl-4H-3,1-benzoxazin-4-ones (3a-o) in excellent yield (Table I). Thus, a solution of 4.0 g of a methyl N-aroylanthranilate (1) in 10 ml of concentrated sulfuric acid is allowed to stand for 20-24 hours and then is mixed with ice and water. Following careful neutralization with aqueous sodium bicarbonate, the precipitated solid is washed thoroughly with water and is dried at room temperature in the air, or under vacuum, to yield the corresponding benzoxazinone (3) in 91-98% yield. The structures of the isolated products are supported by their melting points, in the cases of known compounds, their infrared spectra, which exhibit carbonyl absorption bands at 1750-1760 cm^{-1} (mineral oil mulls),[3] and their proton NMR spectra (Table I). This method is not suitable for the preparation of 2-alkyl-4H-3,1-benzoxazin-4-ones, because of the ease with which these compounds undergo hydrolytic ring opening.[2,3] Thus attempts to prepare 2-benzyl- and 2-cyclohexyl-4H-3,1-benzoxazin-4-one yielded N-phenylacetyl- and N-cyclohexanecarbonylanthranilic acid, respectively, containing only traces of the desired benzoxazinones.

With regard to its mechanism, like the analogous formation of N-substituted 2-amino-4H-3,1-benzoxazin-4-ones,[4] this reaction very likely involves conversion of the ester group of 1 into an acylium ion (2), which undergoes nucleophilic attack by the amide carbonyl oxygen. The intermediacy of a strong electrophilic species is supported by the cyclization of methyl N-(3,5-dinitrobenzoyl anthranilate to the expected benzoxazinone (3o), in contrast to the failure of the similarly N-substituted anthranilic acid to cyclize by the action of acetic anhydride.[2] However, only traces of cyclized product could be detected in the case of methyl N-ethoxalylanthranilate, even after its solution in sulfuric acid had stood for 72 hours. This is presumably due to the decreased electron density at the amide carbonyl oxygen, as a result of the electron withdrawing effect of the adjacent ester carbonyl group. Some steric limitation is indicated by the incomplete cyclization of methyl N-(2,6-dichlorobenzoyl)anthranilate after 20 hours. A good yield of benzoxazinone 3k is obtained when the sulfuric acid solution of 1k is allowed to stand for 48 hours, although the relatively low melting point of the crude product indicates that the reaction is not as clean as in the other cases.

Overall, the reaction described in this communication leads to 2-aryl 4H-3,1-benzoxazin-4-ones in almost quantitative yield and, as a result, is a convenient approach to these synthetically useful compounds.

Table I

2-Aryl-4H-3,1-benzoxazin-4-ones (3)



Compound[a]	R	% Yield[b]	M.p. °C Crude product	M.p. °C Pure compound	^{1}H-NMR[c] (ppm)
3a	Ph	97	118-120	123-124,[d] 123[e]	7.3-7.8(m,5H),8.1-8.4(m,3H)
3b	2-$CH_3C_6H_4$	94	112-113	115,[d] 114[e]	2.7(s,3,CH_3),7.3-8.4(m,8,ArH)
3c	3-$CH_3C_6H_4$	97	112-115	118-120[f]	2.4(s,3,CH_3),7.4-8.3(m,8,ArH)
3d	4-$CH_3C_6H_4$	97	151-153	154.5,[d] 155[e]	2.4(s,3,CH_3),7.3-8.4(m,8,ArH)
3e	4-n-$C_3H_7C_6H_4$	98	80-84	90-91[g]	1.0(t,3,CH_3),1.7(m,2,CH_2),2.7(t,2,CH_2),7.2-8.0(m,5,ArH),8.2-8.3(m,3,ArH)
3f	4-$CH_3OC_6H_4$	97	153-155	148,[e] 158.5[h]	3.9(s,3,CH_3),6.9-7.1(m,2,ArH),7.1-8.0(m,3,ArH),8.2-8.3(m,3,ArH)
3g	2-ClC_6H_4	94	130-133	139-140[d],138[e]	7.3-8.1(m,7H),8.2-8.4(m,1H)
3h	3-ClC_6H_4[i]	97	148-151	156-157[f]	7.3-7.9(m,5H),8.1-8.3(m,3H)
3i	4-ClC_6H_4	96	188-190	190[d,e]	7.3-7.9(m,5H),8.0-8.4(m,3H)
3j	2,4-$Cl_2C_6H_3$	94	128-131	129-130[j]	7.2-8.0(m,6H),8.3-8.4(m,1H)
3k	2,6-$Cl_2C_6H_3$	91	153-159	167-168.5[f]	7.3-8.1(m,6H),8.3-8.4(m,1H)
3l	3,4-$Cl_2C_6H_3$	98	165-167	171-172[k]	7.3-8.4(m,7H)
3m	3-$NO_2C_6H_4$	98	164-166	166,[e] 167-168[l]	7.3-8.1(m,4H),8.2-8.7(m,3H),9.2(m,1H)
3n	4-$NO_2C_6H_4$	92	197-199	203[d,e]	7.4-8.1(m,3H),8.3-8.8(m,5H)
3o	3,5-$(NO_2)_2C_6H_3$[m,n]	92	230-234	234-236[o]	

[a] All new compounds gave satisfactory microanalytical results (C,H,N: ±0.20%). [b] Crude products. [c] Recorded on a Varian EM 360 spectrometer using solutions in deuteriochloroform and tetramethylsilane as internal standard. [d] Reference 2. [e] Reference 3. [f] Recrystallized from ethyl acetate/petroleum ether (b.p. 63-75°). [g] Recrystallized from petroluem ether (b.p. 63-75°). [h] C. L. Arcus and R. E. Marks, J. Chem. Soc., 1956, 1627. [i] W. C. Doyle, Jr. and T. L. Ahle, U.S. Patent 3,650,728; Chem Abstr., 77, P44330b (1972)(m.p. not given). [j] W. Ried and J. Valentin, Chem Ber., 1968, 101, 2106. [k] Recrystallized from acetonitrile. [l] M. T. Bogert, R. A. Gortner, and C. G. Amend, J. Am. Chem. Soc., 1911, 33, 949. [m] L. W. Frost, Canadian Patent 1,031,340; Chem. Abstr., 90, P6876v (1979) (m.p. not given). [n] NMR spectrum not obtained because of lack of solubility. [o] Recrystallized from toluene.

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