fraction (X_{H_2O}) in the stock mixture was predetermined so that the final desired X_{H_2O} in the cuvette solution to be submitted to UV determination was obtained upon mixing ca. 1 mL of Me_2SO with ca. 1 mL of the stock Me_2SO–H_2O mixture.

The sodium methoxide solution in Me_2SO was prepared by mixing in a volumetric flask a known aliquot of a stock methanolic sodium methoxide solution with a weighed amount of anhydrous Me_2SO in such proportions to obtain, after mixing in the cuvette with the Me_2SO solution of the acidic compound, both the desired X_{MeOH} and the desired base concentration. The stock methanolic sodium methoxide solution was prepared at 0 °C from a small weighed amount of clean sodium metal and a weighed amount of CH_3OH.

The tetramethylammonium hydroxide solution in Me_2SO–*t*-BuOH was prepared by mixing in a volumetric flask a weighed amount of $Me_4NOH{\cdot}5H_2O$ with weighed amounts of Me_2SO and *t*-BuOH under conditions quite similar to those described in the preceding paragraph.

UV and visible spectra were recorded as described elsewhere[5] by use of Beckman DB-GT instrument: the cell compartment was thermostated at 25 ± 0.1 °C.

Registry No. 1, 4982-34-7; 2, 838-40-4; 3, 101-17-7; 4, 836-30-6; 5, 4505-48-0; 6, 1961-97-3.

A New Amine Catalyzed Synthesis of 2-Substituted 2,3-Dihydro-4*H*-1,3-benzoxazin-4-ones

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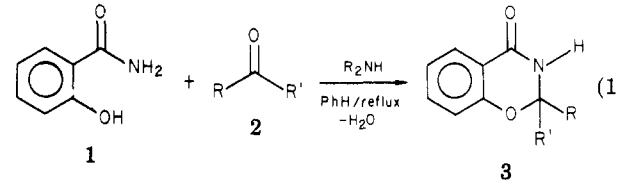
2-Alkyl-, 2,2-dialkyl-, 2-aryl-, and 2-alkyl-2-aryl-2,3-dihydro-4*H*-1,3-benzoxazin-4-ones (**3**, see Table I)[1] are conceptually important because of their similarity in structure to the medicinally interesting benzopyran-4-ones.[2] To date the only method for synthesis of the 2,3-dihydro-4*H*-1,3-benzoxazin-4-one nucleus relies on the acid-catalyzed condensation between suitably substituted salicylamides and aldehydes or ketones.[3]

During the course of a recent synthesis we required the construction of the dihydrobenzoxazin-4-one system on a somewhat complex salicylamide. Not entirely to our surprise, we found that under various acidic reaction conditions the reaction either completely failed or proceeded in only moderate (not synthetically useful) yield. In light of this problem, we began to search for alternate methods (i.e., nonacidic) to synthesize 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones. In order to compare an alternate method with existing literature examples (acid catalyzed) we chose salicylamide as our substrate. Our findings are summarized below and in Table I.

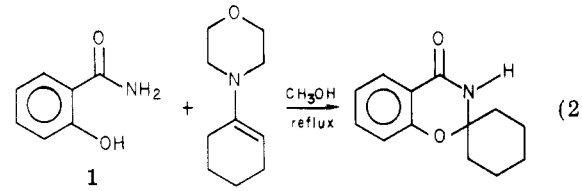
We have found that the condensation between salicylamide (**1**) and aldehydes or ketones (**2**, see Table I) can also be catalyzed by secondary amines[4] (pyrrolidine, morpholine, etc). The reactions are best carried out in refluxing benzene or toluene with 10 mol% amine catalyst. Water is removed from the reaction with the aid of a Dean–Stark trap. In many cases the product of the reaction (**3**, see Table I) crystallizes directly from the reaction



1 2 3 (1)

mixture upon cooling. Filtration of the reaction mixture then gives pure product. Noteworthy is the fact that this new amine-catalyzed reaction generally results in higher yields of the 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones than does the previous acid-catalyzed reaction. An exception to this seems to arise when alkyl aldehydes are used (see Table I, entry 17). For example, the use of acetaldehyde failed to give any of the desired product. The only ketones that failed to undergo reaction, or that gave low yields, were either sterically congested (entry 9), capable of forming stable products with the amine catalyst (entry 11), or involved volatile substrates[5] (entry 1).

It is also interesting that enamines, such as **4**, can also



1 4 5 (94%) (2)

be used as substrates in this reaction and provide the product in a slightly higher yield than that obtained in the catalytic process. N-Substituted salicylamides (i.e., *N*-aryl) fail to undergo reaction with both aldehydes and ketones. The use of an optically active amine catalyst leads to only trace amounts of optical induction.

An excellent alternative to the previous acid-catalyzed synthesis of 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones is now available. It very nicely complements the existing methodology since in many cases higher yields are obtained by utilizing an amine rather than an acid catalyst.

Experimental Section

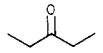
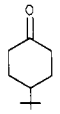
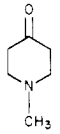
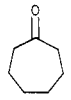
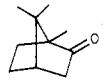
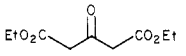
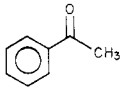
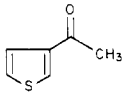
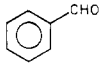
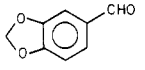
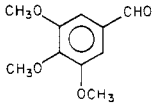
All analytical data, except for NMR spectra, were obtained by the Physical and Analytical Chemistry Department of The Upjohn Company. NMR spectra were obtained at 60 MHz in chloroform-*d* solutions containing tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 197 spectrophotometer in $CHCl_3$ solution or as mulls. Thin-layer chromatography (TLC) was conducted by using Merck glass plates precoated with silica gel 60 F-254. The TLC plates were visualized by UV light or iodine. All solvents were reagent grade distilled in glass (Burdick and Jackson).

(1) J. Finkelstein and E. Chiang, *J. Med. Chem.*, 11, 1038 (1968).
(2) G. P. Ellis, "Chromenes, Chromanones and Chromones", John Wiley and Sons, New York, 1967, pp 345–348, 613, 668, 715, 791, 823, 881, 912, 985, 1063.
(3) A. W. Titherley, *J. Chem. Soc.*, **91**, 1425 (1907); C. A. Keane and W. W. S. Nicholls, *ibid.*, 266 (1907); E. Glaser and S. Frisch, *Arch. Pharm.*, **266**, 103 (1928); H. P. Kaufmann, *ibid.*, **265**, 266 (1927); W. L. Hicks, *J. Chem. Soc.*, **97**, 1032 (1910); V. Moucka and C. Royl, *Chem. Ber.*, **59**, 756 (1926); A. W. Titherley and E. C. Hughes, *J. Chem. Soc.*, **97**, 1368 (1910); *ibid.*, **99**, 23 (1911); N. W. Hirwe and K. N. Rana, *Chem. Abstr.*, **34**, 2819 (1940); K. N. Rana, *J. Indian Chem. Soc.*, **19**, 299 (1942); H. O. Fischer, G. Dangschat, and H. Slettiner, *Chem. Ber.*, **65**, 1032 (1932); D. T. Mowry, W. H Yanko, and E. L. Ringwald, *J. Am. Chem. Soc.*, **69**, 2358 (1947); B. W. Horrom and H. E. Zaugg, *ibid.*, **72**, 721 (1950); J. L. Irvine and C. Piantadosi, *Synthesis*, 568 (1972); T. Kametani, T. Higa, C. V. Loc, M. Ihara, and K. Fukumoto, *Heterocycles*, **6**, 255 (1977); M. Covello, F. DeSimone, and E. Abignete, *Ann. Chim. (Rome)*, **59**, 367 (1969).

(4) For a similar reaction that results in the synthesis of 2-substituted-4*H*-chromanones see H. J. Kabee, *Synthesis*, 886 (1978).
(5) The low yield resulting from the reaction with acetone appeared to be due to the low boiling point of acetone and perhaps the inability to separate the water from the acetone efficiently. A number of drying agents (K_2CO_3, alumina, $MgSO_4$, $CaCl_2$) were employed but yields were not dramatically improved. The use of 3-Å molecular sieves did afford the acetone adduct in 50% after heating at reflux in a 1:1 mixture of benzene/acetone for 4 days.

0022-3263/81/1946-3340$01.25/0

Table I. Amine-Catalyzed Reaction between Salicylamide and Aldehydes and Ketones

entry	ketone/aldehyde	mp,[d] °C (lit. mp, °C)	% yield	lit. % yield
1		135-137[e] (135-137[c])	41, 50,[4] (80)[a]	89[c]
2		99-100[f] (101-102[c])	92	18[c]
3		138.8-139.7[g] (135-137[d])	82	72[c]
4		191.9-193.0[h] (188-190[c])	85 (94)[b]	92[c]
5		208-215[i]	92	
6		192.3-193.8[i]	89	
7		194.6-195.0[i] (192-193[c])	89	87[c]
8		155.1-156.8[h]	81	
9			no reaction	
10		177.2-178.0[i]	98	
11			no reaction	
12		227-228[i] (226-227[c])	92	38[c]
13		179.5-181.1[h]	48	
14		168-169[j] (168-169[c])	85	89[c]
15		200.8-202.9[i] (199-200[c])	78	32[c]
16		173.6-174.0[i]	83	
17	C_4H_9CHO	77-79[e]	28	

[a] Yield based on recovered salicylamide. [b] Yield from refluxing 1 and the morpholino enamine of cyclohexanone in CH_3OH. [c] B. W. Horrom and H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 721 (1950). [d] Method of purification or recrystallization solvent. [e] Silica gel chromatography, 25% EtOAc/hexane. [f] Hexane. [g] EtOAc/hexane. [h] EtOAc. [i] Collected by filtration from the reaction. [j] 95% EtOH.

Typical Procedure. 2,3-Dihydro-2,2-diethyl-4*H*-1,3-benzoxazin-4-one (Entry 2). To a benzene solution (130 mL) of salicylamide (5.28 g, 38.5 mmol) and 3-pentanone (12.2 mL, 115.5 mmol), under nitrogen, was added pyrrolidine (0.3 mL, 3.6 mmol). That mixture was heated at reflux with azeotropic removal of water for 18 h. The reaction was cooled, washed with 2 N HCl, and then dried over $MgSO_4$. Removal of solvent in vacuo afforded a white solid which, after recrystallization from hexane, gave 7.23 g of the product (92% yield): mp 99–100 °C; IR (mull) 3160, 3060 (NH), 1675 (C=O), 1250, 965, 760 (C=C, other) cm^{-1}; NMR ($CDCl_3$) δ 8.63–8.33 (br m, 1 H), 7.96 (dd, J = 8, 2 Hz, 1 H), 7.63–6.95 (m, 3 H), 1.94 (q, J = 8 Hz, 4 H), 1.0 (t, J = 8 Hz, 6 H); mass spectrum, m/e (relative intensity) 205 (parent, 14), 176 (100), 121 (78), 92 (12), 85 (14). Anal. Calcd for $C_{12}H_{15}NO_2$ (mol wt 205): C, 70.22; H, 7.36; N, 6.82. Found: C, 70.36; H, 7.22; N, 7.03.

2,3-Dihydro-2,2-dimethyl-4*H*-1,3-benzoxazin-4-one (Entry 1). Salicylamide (5.64 g, 41.1 mmol) was combined with acetone

(75 mL) and benzene (80 mL), and pyrrolidine (3.5 mL, 42 mmol) was added. This mixture was heated at reflux under nitrogen for 24 h. During the reflux period, the refluxing solvent was percolated through K_2CO_3. The reaction mixture was cooled, concentrated in vacuo to ~50 mL, and diluted with EtOAc (150 mL). This mixture was then extracted with 2 N NaOH (2 × 75 mL), 2 N HCl (3 × 75 mL), and brine (1 × 25 mL). The resulting organic layer was dried ($MgSO_4$) and solvent removed in vacuo to give a dark viscous oil. Silica gel chromatography (1 kg, 25% EtOAc/hexane) afforded 3.0 g (41%) of the desired product. The basic extract of the crude reaction mixture gave, upon acidification, 2.7 g of salicylamide. Based on recovered starting material the yield is calculated as 80%: mp 135 °C; IR (mull) 3180, 3080 (NH), 1680 (C=O), 1615, 1585 (C=C) 1260, 1150, 755 (C—O/other) cm^{-1}; NMR ($CDCl_3$) δ 8.2–7.9 (m, 2 H), 7.65–6.80 (m, 3 H), 1.66 (s, 6 H). Anal. Calcd for $C_{10}H_{11}NO_2$ (mol wt 177): C, 67.78; H, 6.25; N, 7.90. Found: C, 67.73; H, 6.23; N, 7.83.

Acknowledgment. The technical assistance of P. M. Gold is gratefully acknowledged.

Registry No. Salicylamide, 65-45-2; acetone, 67-64-1; 3-pentanone, 96-22-0; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 4-*tert*-butylcyclohexanone, 98-53-3; tetrahydro-(4*H*)-thiopyran-4-one, 1072-72-6; 1-methyl-4-piperidinone, 1445-73-4; cycloheptanone, 502-42-1; cyclododecanone, 830-13-7; 1-phenylethanone, 98-86-2; 1-(3-thienyl)ethanone, 1468-83-3; benzaldehyde, 100-52-7; 5-carboxaldehyde-1,3-benzodioxole, 120-57-0; 3,4,5-trimethoxybenzaldehyde, 86-81-7; pentanal, 110-62-3; 2,3-dihydro-2,2-dimethyl-4*H*-1,3-benzoxazin-4-one, 30914-88-6; 2,3-dihydro-2,2-diethyl-4*H*-1,3-benzoxazin-4-one, 77773-92-3; spiro-[2*H*-1,3-benzoxazine-2,1'-cyclopentan]-4(3*H*)-one, 40033-94-1; spiro[2*H*-1,3-benzoxazine-2,1'-cyclohexan]-4(3*H*)one, 40033-95-2; 4'-(1,1-dimethylethyl)-spiro[2*H*-1,3-benzoxazine-2,1'-cyclohexan-4(3*H*)-one], 77773-93-4; 2',3',5',6'-tetrahydro-spiro-[2*H*-1,3-benzoxazine-2,4'-[4*H*]thiopyran]-4(3*H*)-one, 77773-94-5; 1'-methylspiro[2*H*-1,3-benzoxazine-2,4'-piperidin]-4-(3*H*)-one, 77773-95-6; spiro[2*H*-1,3-benzoxazine-2,1'-cycloheptan]-4-(3*H*)-one, 77773-96-7; spiro[2*H*-1,3-benzoxazine-2,1'-cyclododecan]-4(3*H*)-one, 77773-97-8; 2,3-dihydro-2-methyl-2-phenyl-4*H*-1,3-benzoxazin-4-one, 40033-93-0; 2,3-dihydro-2-methyl-2-(3-thienyl)-4*H*-1,3-benzoxazin-4-one, 77773-98-9; 2,3-dihydro-2-phenyl-4*H*-1,3-benzoxazin-4-one, 6629-80-7; 2,3-dihydro-2-(1,3-benzodioxol-5-yl)-4*H*-1,3-benzoxazin-4-one, 77773-99-0; 2,3-dihydro-2-(3,4,5-trimethoxyphenyl)-4*H*-1,3-benzoxazin-4-one, 52942-53-7; 2,3-dihydro-2-butyl-4*H*-1,3-benzoxazin-4-one, 77774-00-6.

Supplementary Material Available: Full experimental details for entries 3–17 in Table I (4 pages). Ordering information is given on any current masthead page.

Kinetics and Mechanism for *o*-Hydroxybenzaldehyde Phenylhydrazone Formation

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Benzaldehyde phenylhydrazone formation occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under neutral or basic conditions[2] (see eq 1 and 2). The addition of phenylhydrazine to form the

$$RNH_2 + C{=}O \underset{}{\overset{k_H}{\rightleftharpoons}} RNH{-}C{-}OH \underset{k_2}{\xrightarrow{k_1 a_H}} RN{=}C + H_2O \quad (1)$$

$$K_{ad} = \frac{[RNH{-}C{-}OH]}{[RNH_2][C{=}O]} \quad (2)$$

carbinolamine from this substrate is subject to both specific-acid and general-acid catalysis by carboxylic acid (α = 0.35). The dehydration step is subject to acid catalysis although pH-independent and base-catalyzed processes also occur.[2]

The rates of reaction of several ortho-substituted benzaldehydes, with substituents that are not capable of formation of a hydrogen bond with the carbonyl group, with phenylhydrazine have been studied.[3]

A detailed study of the kinetics of phenylhydrazone formation from *o*-hydroxybenzaldehyde was undertaken in order to examine the effects on reactivity toward nucleophiles of an ortho substituent capable of formation of a hydrogen bond with the oxygen of the carbonyl group of the aldehyde.

Experimental Section

Materials. All reagents employed were obtained commercially and, with exception of reagent grade inorganic salts, were either redistilled or recrystallized before use. Solutions of phenylhydrazine were prepared just prior to use.

Kinetics measurements were carried out spectrophotometrically at 25.0 °C with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell holder through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the phenylhydrazone at 347 nm, with an initial concentration of *o*-hydroxybenzaldehyde of 3.3×10^{-5} M. In all cases a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from slopes of plots of log ($OD_\infty - OD_t$) against time in the usual manner.

It was difficult to determine spectrophotometrically the equilibrium constant for the formation of the carbinolamine from the *o*-hydroxybenzaldehyde and phenylhydrazine as a result of the strong light absorption of the latter substance. Similar difficulties have been noted in attempts to determine the equilibrium constants for the formation of other phenylhydrazine carbinolamines.[2,4] With *o*-hydroxybenzaldehyde the reaction is first order in phenylhydrazine concentration over the concentration range 1.0×10^{-3} to 5.0×10^{-3} M at pH 7. Consequently, all kinetic studies have been made by employing a phenylhydrazine concentration lower than 5.0×10^{-3} M. Second-order rate constants could therefore be determined by directly dividing first-order rate constants by the concentration of phenylhydrazine free base.

All kinetic experiments were carried out in 20% aqueous ethanol at an ionic strength of 0.50, maintained with KCl, with 2.0×10^{-4} M EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculations of the concentrations of phenylhydrazine free base and of undissociated carboxylic acids were made employing the Henderson–Halsselbalch equation and values of pK_a from ref 3 and 5.

pK_a Determinations. The value of pK_a of *o*-hydroxybenzaldehyde was obtained at 25.0 °C in 20% aqueous ethanol and at an ionic strength of 0.50, maintained with KCl, with a Zeiss PMQ II spectrophotometer by measuring the effect of pH on the absorption of light at 379 nm (Table I, supplementary material). Plots of $E^- - OD/[H^+]$ against OD yield a pK_a of 8.42.

Results and Discussion

In Figure 1, logarithms of second-order rate constants for the reaction of phenylhydrazine with *o*-hydroxybenzaldehyde in 20% aqueous ethanol at 25.0 °C and an ionic strength of 0.50 are plotted as a function of pH. The curve

(1) Fellow of the Fundação de Amparo à Pesquisa do Estado de São Paulo.
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