Cl, 19.00.

2-Ethoxycarbonyl-4-oxo-1-phenylpyridazine (18). To a solution of ethyl 2-phenylazoacetoacetate (4.69 g, 20 mmol) in DMF (15 mL) was added BBDM (10 mL) and the mixture was heated at 70 °C overnight. The mixture was then evaporated in vacuo and the residue was chromatographed on 85 g of silica gel with petroleum ether (30–60 °C)–ethyl acetate (1:2) to give, from evaporation of the proper fractions, pyridazinone **18** as a colorless oil (4.24 g, 87%) which spontaneously crystallized on standing. Recrystallization from ethanol afforded an analytically pure sample: mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, CH_3), 4.43 (q, 2 H, CH_2), 6.74 (d, 1 H, H-5, $J_{5,6}$ = 7.9 Hz), 7.45–7.56 (m, 5 H, C_6H_5), 8.33 (d, 1 H, H-6). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.88; H, 5.01; N, 11.39.

Preparation of 14 from 18. A mixture of **18** (3 g, 12.3 mmol), guanidine carbonate (3.3 g, 18.3 mmol), and ethanol (40 mL) was heated to reflux with stirring for 4 h and then cooled in a ice bath. The precipitate was collected and washed thoroughly with cold water to afford **14** (2.5 g, 85%) identical in all respects with an authentic sample prepared from **12** (vide supra).

Preparation of 14 from 12 with Triethyl Orthoformate. A mixture of **12** (229 mg, 1 mmol), triethyl orthoformate (5 mL), and trifluoroacetic acid (2 mL) was stirred overnight at room temperature. To the yellow suspension was added 15 mL of ethyl ether. After stirring for 20 min, the solid was collected by filtration to afford **14** (309 mg, 87.4%) as its analytically pure trifluoroacetate salt: mp >300 °C; UV (pH 1) λ_{max} 203 (ϵ 23 210), 260 (10 000), 328 (shoulder) (16 430), 362 nm (22 500), λ_{min} 241 (ϵ 8 210), 288 nm (7 500); (pH 7) λ_{max} 203 (ϵ 21 100), 292 (18 210), 376 nm (15 000), λ_{min} 247 (ϵ 3 930) 325 nm (6 790); (pH 13) 218 (ϵ 15 000), 292 (22 500), 376 nm (18 210), λ_{min} 247 (ϵ 5 000), 325 nm (8 930). Anal. Calcd for $C_{12}H_9N_5O$:CF_3COOH: C, 47.57; H, 2.83; N, 19.82; F, 16.14. Found: C, 47.60; H, 2.92; N, 19.90; F, 16.17.

Registry No.—**1**, 14985-77-4; **2**, 23947-86-6; **4**, 65996-47-6; **5**, 65996-48-7; **6**, 15020-66-3; **7**, 65996-49-8; **8**, 65996-50-1; **9**, 6270-46-8; **10**, 65996-51-2; **11**, 65996-52-3; **12**, 65996-53-4; **13**, 65996-54-5; **14**, 65996-55-6; **14** HCl, 65996-56-7; **14** CF_3COOH salt, 65996-57-8; **15**, 65996-58-9; **15** HCl, 65996-59-0; **16**, 5462-33-9; **18**, 65996-60-3; BBDM, 5815-08-7.

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(1) This investigation was supported in part by funds awarded by the National Cancer Institute, DHEW (Grants No. CA-08748, and CA-18856), and a Fellowship (to M.I.L.) from the Westchester Division of the American Cancer Society.
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Notes

Synthesis of γ-Amino Alcohols

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Received December 9, 1977

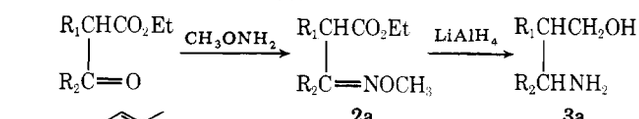
Substituted γ-amino alcohols have been of considerable interest for some time in that they frequently possess interesting pharmacological properties.[1] Their synthesis has been accomplished by a variety of procedures: addition of ammonia or amines to acrylic esters or α,β-unsaturated ketones, followed by reduction;[1b,2] reduction of α-cyano esters;[3] the reduction of isoxazoles or isoxazolines;[4] reduction of Mannich products;[5] and reaction of bromo alcohols with sodium azide followed by reduction.[6] All of these methods suffer from certain restrictions. Addition of amines to acrylates frequently leads to the formation of amides as side products. The reduction of cyano esters precludes preparation of compounds bearing a substituent α to the nitrogen. The synthesis of isoxazoles or isoxazolines is often a difficult undertaking. The Mannich reaction is restricted to the preparation of tertiary amines. Lastly the use of the azide procedure assumes the availability of the precursor bromo alcohol.

In this note we describe a new method for the synthesis of γ-amino alcohols, utilizing 1,3-dicarbonyl compounds as starting materials, which circumvents many of the problems that detract from established procedures.

The ease of preparation of α-formyl and β-keto esters makes them attractive intermediates for the synthesis of γ-amino alcohols. Unfortunately, nitrogen functionality cannot be introduced via oxime formation since the intermediate oximino ester cyclizes spontaneously to an isoxazolone which cannot be reductively cleaved.[7] Use of an alkoxime, however, avoids cyclization since a blocked oximino ester is formed which can then be reduced to give the desired amino alcohol (Scheme I).

The methoxylimine **2a** of ethyl 2-formyl-2-(3-pyridyl)-acetate (**1a**) was reduced with $LiAlH_4$ to the γ-amino alcohol

Scheme I



1a, R_1 =  ; R_2 = H	**2a**	**3a**
b, R_1 = $C_6H_5CH_2$; R_2 = H	**b**	**b**
c, R_1 = C_6H_5; R_2 = H	**c**	**c**
d, R_1 = H; R_2 = C_6H_5	**d**	**d**
e, R_1 = H; R_2 = 	**e**	**e**

0022-3263/78/1943-2539$01.00/0

3a in 64% overall yield from **1a**. Although $LiAlH_4$ reduction of oximes β to an aromatic ring is frequently accompanied by side products,[8] particularly aziridines, no such complication was observed in the preparation of **3a–d**. An inability to purify amino alcohol **3a** by either distillation or crystallization prompted its derivatization as the ditosylate which gave spectral data consistent with the assigned structure. The syntheses of 2-benzyl-3-amino-1-propanol (**3b**) and 2-phenyl-3-amino-1-propanol (**3c**) were also achieved by an analogous sequence in yields of 90 and 42%, respectively.

The preparation of a 3-substituted 3-amino-1-propanol was then carried out via a similar synthetic pathway using a β-keto ester as the starting material (Scheme I). Treatment of ethyl benzoylacetate (**1d**) with *O*-methylhydroxylamine hydrochloride and base gave a 75% yield of **2d**. Reduction of **2d** with $LiAlH_4$ gave a crystalline product in 79% yield with spectral data consistent with **3d**.

Application of this scheme to the 3-pyridyl β-keto ester **1e** was unsuccessful. Preparation of methoxylimine **2e** followed by its reduction under a variety of conditions led to a complex mixture of products. Treatment of the crude reaction mixture in each case with tosyl chloride and comparison of the products, using TLC, with the authentic ditosylate of **3e**[9] showed only trace amounts of material corresponding to the ditosylate of the desired amino alcohol.

In summary, we have described a two-step procedure for the preparation of substituted γ-amino alcohols from readily available starting materials.

Experimental Section

All of the melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Varian A-60A spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer No. 621 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Ethyl 2-Formyl-2-(3-pyridyl)acetate (1a). A mixture of 25 g (0.151 mol) of ethyl 3-pyridylacetate and 6.6 g (0.151 mol) of 55% NaH dispersion in 250 mL of benzene was heated under reflux for 30 min and then treated with 25 mL of ethyl formate after cooling to 15 °C. After being stirred for 1 h at 15 °C and being heated under reflux for 45 min, the solution was cooled to 5 °C and 87 mL of an ice-cold solution of dilute HCl (6.35%, 0.151 mol) was added. The separated benzene phase was concentrated to give a solid which was collected, washed with ether, and dried in vacuo to afford 23 g (80%) of **1a**, mp 121–125 °C. Recrystallization from benzene gave the analytical sample, mp 122–123 °C. This compound is relatively unstable and should be used without delay: IR (tf) 2470 (enol), 1702 cm^{-1} (ester); ^{1}H NMR (Me_2SO-d_6) δ 1.20 (t, 3, J = 7 Hz, CH_3), 4.13 (q, 2, J = 7 Hz, CH_2), 7.33 (m, 1, 5-PyH), 7.68 (dt, 1, J = 8, 2, 2, Hz, 4-PyH), 8.02 (s, 1, C=C*H*OH), 8.40 (dd, 1, J = 5.5, 2 Hz, 6-PyH), 8.55 (d, 1, J = 2 Hz, 2-PyH). Anal. ($C_{10}H_{11}NO_3$): C, H, N.

Ethyl 2-(3-Pyridyl)-3-methoxyliminopropionate (2a). A mixture of 36.8 g (0.44 mol) of $NaHCO_3$ and 36.2 g (0.43 mol) of *O*-methylhydroxylamine hydrochloride in 1.5 L of methanol was agitated until gas evolution ceased. The mixture was cooled to 5 °C and 81.8 g (0.42 mol) of **1a** was added. The reaction mixture was stirred for 12 h at room temperature and concentrated to a small volume under reduced pressure and the residue was distributed between water and CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and distilled (114–116 °C (0.15 mm)) to give 74.0 g (78.5%) of **2a**: IR (neat) 1750 (ester), 1590, 710 cm^{-1} (pyridine). Anal. ($C_{11}H_{14}N_2O_3$): C, H, N.

2-(3-Pyridyl)-3-amino-1-propanol (3a). To a slurry of 17.45 g (0.46 mol) of $LiAlH_4$ in 1 L of 1,2-dimethoxyethane was added 22.65 g (0.10 mol) of **2a** over 2.5 h. The temperature was maintained from −5 to 0 °C during the addition. The reaction mixture was then stirred for 5 days at room temperature, cooled to 0 °C, and slowly combined with 85 mL of saturated brine. After being stirred for 4 h, the mixture was filtered and concentrated at reduced pressure and the resulting oily residue was dried by azeotroping with benzene and ethanol. After concentration, 11.50 g (74%) of crude **3a** was obtained as a viscous yellow oil.

A solution of 11.5 g (0.0755 mol) of **3a** in 115 mL of dry pyridine was cooled to 0 °C and treated with 31.7 g (0.1655 mol) of tosyl chloride. The reaction mixture was stirred at 0 °C for 22 h and then diluted with ice water. The aqueous portion was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to give 28.85 g (83%) of crude ditosylate, mp 150–153 °C. An analytical sample was obtained by chromatography on silica gel followed by recrystallization from acetonitrile: mp 170–170.5 °C; IR (nm) 3180 (NH), 815, 710 cm^{-1} (pyridine); ^{1}H NMR (Me_2SO-d_6) δ 2.36 (s, 3, CH_3), 2.40 (s, 3, CH_3), 3.02 (m, 3, CH + CH_2N), 4.26 (br d, 2, J = 4 Hz, CH_2O), 7.48 (m, 10, phenyl + 4,5-PyH), 8.30 (m, 2, 2,6-PyH). Anal. ($C_{22}H_{24}N_2O_5S_2$): C, H, N, S.

Ethyl 2-Benzyl-3-methoxyliminopropionate (2b). Ethyl 2-*formylhydrocinnamate*[10] (6.0 g, 29.1 mmol) was added to a stirred solution of 60 mL of dry pyridine containing 2.49 g (29.8 mmol) of *O*-methylhydroxylamine hydrochloride. The reaction mixture was heated at 70 °C for 18 h and worked up as before to give 6.73 g of crude product. Distillation (105–107 °C (0.1 mm)) gave 5.80 g (86%) of **2b**: IR (neat) 1740 (ester), 1610, 1590, 745 cm^{-1} (phenyl). Anal. ($C_{13}H_{17}NO_3$): C, H, N.

2-Benzyl-3-amino-1-propanol (3b). To a slurry of 482 mg (12.75 mmol) of $LiAlH_4$ in 50 mL of 1,2-dimethoxyethane was added 1.0 g (4.25 mmol) of **2b**. The reaction mixture was heated under reflux for 1.5 h, cooled to 0 °C, treated with 2.5 mL of saturated brine, heated at 60 °C for 1 h, and worked up as described for **3a** to give 680 mg (98%) of crude **3b**. A 316-mg sample of **3b** was treated with 173 mg of oxalic acid in 3 mL of absolute EtOH to give 372 mg (92%) of the oxalate, mp 149–150 °C (lit.[3d] mp 150–152 °C).

Ethyl 2-Phenyl-3-methoxyliminopropionate (2c). The preparation of **2c** was carried out using the procedure described for **2b** from 3.52 g (42.0 mmol) of *O*-methylhydroxylamine hydrochloride and 8.0 g (41.7 mmol) of ethyl 2-formyl-2-phenylacetate in 60 mL of pyridine. The yield of distilled (83–84 °C (0.05 mm)) product was 8.21 g (89%): IR (neat) 1740 (ester) 1605, 1590, 750 cm^{-1} (phenyl). Anal. ($C_{12}H_{15}NO_3$): C, H, N.

2-Phenyl-3-amino-1-propanol (3c). The preparation of **3c** was carried out using the procedure described for **3a** from 1.0 g (4.52 mmol) of **2c** and 513 mg (13.5 mmol) of $LiAlH_4$ in 5 mL of glyme. The crude product was isolated as its hydrochloride salt (358 mg. 42%): mp 152–153 °C; IR (nm) 3210 (OH), 1610, 1595, 755 cm^{-1} (phenyl); ^{1}H NMR (D_2O) δ 3.23 (m, 3, CH_2N + CH), 3.74 (br d, 2, J = 5.5 Hz, CH_2O), 7.20 (s, 5, C_6H_5). Anal. ($C_9H_{14}ClNO$): C, H, Cl, N.

Ethyl 3-Phenyl-3-methoxyliminopropionate (2d). The preparation of **2d** was carried out using the procedure described for **2b** from 880 mg (10.55 mmol) of *O*-methylhydroxylamine hydrochloride and 2.0 g (10.4 mmol) of ethyl benzoylacetate (**1d**) in 20 mL of pyridine. The yield of distilled (117–120 °C (0.1 mm)) product was 1.75 g (76%); IR (neat) 1740 (ester), 1625, 1595, 760 cm^{-1} (phenyl). Anal. ($C_{12}H_{15}NO_3$): C, H, N.

3-Amino-3-phenyl-1-propanol (3d). The preparation of **3d** was carried out using the procedure described for **3b** from 1.0 g (4.5 mmol) of **2d** and 512 mg (13.5 mmol) of $LiAlH_4$ in 25 mL of glyme. The reaction was heated under reflux for 2 h. A solid product was isolated which was recrystallized from benzene to give 540 mg (79%) of **3d**, mp 72–73 °C (lit.[2d] mp 74.5–75 °C).

Ethyl 3-(3-Pyridyl)-3-methoxyliminopropionate (2e). To a solution of 2.16 g (25.9 mmol) of *O*-methylhydroxylamine hydrochloride in 25 mL of MeOH was added 2.18 g (25.9 mmol) of $NaHCO_3$. The solution was stirred for 1 h at room temperature and then filtered. The filtrate was added to a solution of 5 g (25.9 mmol) of ethyl nicotinoylacetate[11] (**1e**) in 25 mL of MeOH at 0 °C. The reaction mixture was worked up as described for **2a** after stirring at 0 °C for 20 h and distilled (116–118 °C (0.15 mm)) to give 4.09 g (71%) of **2e**: IR (neat) 1735 (ester), 1605, 1585, 1555, 805, 705 cm^{-1} (pyridine). Anal. ($C_{11}H_{14}N_2O_3$): C, H, N.

Registry No.—**1a**, 62247-40-9; **1b**, 2016-00-4; **1c**, 17838-69-6; **1d**, 94-02-0; **1e**, 6283-81-4; *E*-**2a**, 66102-59-8; *Z*-**2a**, 66102-60-1; *E*-**2b**, 66102-61-2; *Z*-**2b**, 66102-62-3; *E*-**2c**, 66102-63-4; *Z*-**2c**, 66102-64-5; *E*-**2d**, 66102-65-6; *Z*-**2d**, 66102-66-7; *E*-**2e**, 66102-67-8; *Z*-**2e**, 66102-68-9; **3a**, 62247-29-4; **3a** ditosylate, 62247-30-7; **3b**, 66102-69-0; **3b** oxalate, 66102-70-3; **3c** HCl, 21464-48-2; **3d**, 14593-04-5; ethyl 3-pyridylacetate, 39931-77-6; ethyl formate, 109-94-4; *o*-methylhydroxyamine hydrochloride, 593-56-6.

Supplementary Material Available: Full NMR data for compounds **2a–e** (2 pages). Ordering information is given on the masthead page.

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Transformations of *N*-Hydroxyimides.[1] Mechanistic Aspects of the Reaction between *N*-Hydroxyimides, Phenols, Diethyl Azodicarboxylate, and Triphenylphosphine

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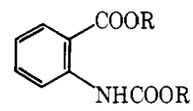
Received December 27, 1977

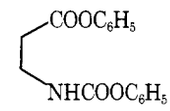
Recently it has been shown that the reaction of alcohols with *N*-hydroxyphthalimide in the presence of equimolar amounts of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) leads to *N*-alkoxyphthalimides.[1a] Under the same conditions alcohols react with phenols to give alkyl aryl ethers.[2] These observations suggested the possibility of a direct route to *N*-aryloxyphthalimides through arylation of *N*-hydroxyphthalimide with phenols. In this paper we present our studies on the reactions of *N*-hydroxyphthalimide and *N*-hydroxysuccinimide with phenols in the presence of DEAD and TPP.

As a result of the reaction of equimolar amounts of *N*-hydroxyphthalimide, phenol, DEAD, and TPP in tetrahydrofuran as solvent, instead of the expected *N*-phenoxyphthalimide, we obtained phenyl *N*-phenoxycarbonylanthranilate **1**, whose properties (cf. Table I and Experimental Section) were identical with those of a substance obtained earlier in the reaction of *N*-hydroxyphthalimide-*O*-triflate with sodium phenoxide.[3] Likewise, phenyl *N*-phenoxycarbonyl-β-alanate **5** obtained in this laboratory displayed identical properties with those of the compound described by Chapman.[3] Compounds **2**, **3**, and **4** were also obtained by the above procedure.

Under conditions of equimolar amounts of substrates the reaction yield did not exceed 30%; this became understandable after the structure of products had been established. When the proportion of substrates was changed so that per 1 mol of *N*-hydroxyimide, 1 mol of DEAD, 1 mol of TPP, and 2 mol of phenol were used, the reaction yields increased about twofold (Table I). We suggest the reaction mechanism in Scheme I.



1, R = C_6H_5
2, R = p-$C_6H_4CH_3$
3, R = p-$C_6H_4OCH_3$
4, R = p-C_6H_4Br



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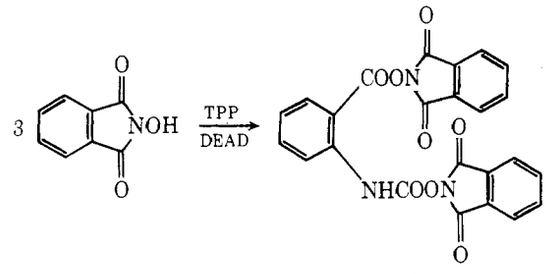
At the first stage betaine I, postulated by Morrison,[4] is formed and gives with *N*-hydroxyphthalimide present in the reaction mixture ion pair II. We postulate an equilibrium between ion pairs II and III;[5] this postulate is based on our earlier observations of the properties of *N*-hydroxyphthalimide which in the presence of other reagents in the discussed type of reaction plays the part of a nucleophilic agent (e.g., in the reaction with alcohols[1a]) or of a electrophilic agent (e.g., in the reaction with carboxylic acids[1c]). Such a nature of *N*-hydroxyphthalimide was confirmed experimentally; namely, the reaction of *N*-hydroxyphthalimide (3 mol) with DEAD (1 mol) and TPP (1 mol) afforded **6** in high yield.



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At the next stage of the suggested mechanism, as a result of reaction with a phenol molecule, ion pair III is transformed into a new ion pair IV accompanied by formation of a molecule of diethyl hydrazodicarboxylate. Subsequently the phenolate anion attacks the carbonyl group, thus causing the opening of the imide ring, Lossen rearrangement to isocyanate, and reaction with the second molecule of phenol. The results of the reaction confirm that $OPPh_3$ is a very good leaving group (cf. structure V), being transformed into the neutral molecule of phosphine oxide. All our observations supporting the proposed reaction mechanism are in agreement[7] with the results of Chapman obtained for the nucleophilic reactions of *N*-hydroxyimide-*O*-triflates[3] and with the results of Bittner concerning the Lossen rearrangement of hydroxamic acids in the presence of betaine I.[6] In addition, it has to be stressed that the occurrence of steric hindrance in phenols either greatly

Table I. Products of the Title Reactions

Compd	Registry no.	Yield, %	Mp, °C	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1	33067-24-2	69	95–96	72.1	4.5	4.2	72.2	4.6	4.4
2	65956-55-0	75	147–148	73.1	5.3	3.9	73.1	5.3	3.9
3	65956-56-1	72	123–124	67.1	4.9	3.6	66.7	4.9	3.6
4	65956-57-2	68	155–156	48.9	2.7	2.9	48.8	2.8	3.0
5	41580-56-7	75	82–83	67.4	5.3	4.9	67.5	5.4	4.8
6	65956-58-3	61	192–193	61.2	2.8	8.9	61.2	2.7	8.9

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